Volume 99 Number 1

January 1980

American Heart Jour

An international publication for the study of the circ"

Contents on

Publisher

S. N MEDICAL COLLEGE,
R A Y.
14334

Haynes Ave

ations: Based on a review of this drug by The National Academy
iences—*National Research Council and/or other information*.
has classified the indications as follows:
robably" effective: The chewable dosage form of SORBITRATE
licated for the treatment of acute anginal attacks and for prophy-
in situations likely to provoke such attacks.
al classification of the less-than-effective indications requires
er investigation.

Up

American Heart Journal

Contents

continued on page

Vol 99 No 1 January 1980 The American Heart Journal is published monthly by The C V Mosby Company 11830 Westline Industrial Drive St Louis Mo 63141

Annual subscription rates

	U.S	*All foreign countries*
Institutional	$4 00	$5 00
Personal†	$ 8 00	$38 00
Student resident†	$2 40	$32.40

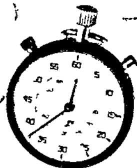
Single copies are $4.50 postpaid Remittances should be made by check draft, post office or express money order payable to this Journal.

Institutional (multiple reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics city county state provincial and national government bureaus and departments and all commercial and private institutions and organizations.
†Personal subscriptions and all student rate subscriptions must be in the names of billed to and paid by individuals All student rate requests must indicate training status and name of institution.
Subscriptions may begin at any time
Second class postage paid at St. Louis Mo and additional mailing offices.

Contents *continued*

continued on

BURDICK



Burdick introduces the -second electrocardiogram.

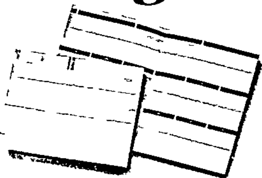
fact only 37 4 seconds to record the complete 12 lead electro-
It s the new EK 8 Burdick s first fully automatic single-channel
ograph

with its new and unique mounting system the EK 8 assures
ECG productivity substantial savings of time for operator and staff
savings on ECG paper

lead is recorded in proper sequence — with lead lengths and
itching on every lead automatically controlled With proper technic
no stopping to move the chest lead fewer overruns less waste
CG s per roll That means additional savings

savings of technician and staff time are possible with the
mounting system Leads are automatically identified and
ete 12 lead tracing is ready for mounting on Burdick self adhesive
folder formats ready for filing In the folder mode with longer
r additional data, the complete ECG is recorded in 47 1 seconds
override provides full choice of lead lengths if desired

new faster Burdick EK 8 Because time is your valuable asset for
ent service For more information or a demonstration call us
at 800 356-0701 In ... call 608 868 7631 ...



Burd ck card and folder format mounts — fast eff cient way to mount and f le ECGs



Contents *continued*

(Information for authors on page 13)
(Index to advertisers on page 40)

February 1980

American Heart Journal

Copyright © 1980 by The C V Mosby Company

Contents

continued on page "

Vol. 99 No ? February 1980 Th Ameri n Heart Journal is published monthl by Th C V Mosby Company 11830 Westline Indu tri l Drive St Louis, Mo 63141

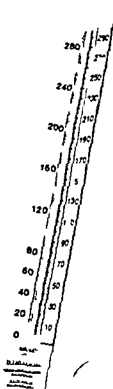
Annual subscription rates

	U S	*All foreign countries*
Institutional	$4 00	$55 00
Personal†	$_8 00	$38.00
Student, resid nt†	$?? 40	$3_40

Single copies are $4 50 postpaid *Remittances should be made by check, draft* post office or press money order p vable to this Journal

Institutional (multiple-reader) subscriptions are av lable to publ and pri ate libraries schools, hosp tals, and cl nics city county state provincial and n tional go ernment bureaus an l departments and all comm rcial and pri at institut ons and organizations
†P rsonal s bscriptions and all student rate subscriptions must be in the names of billed to and paid by individual All student rate requests must indicate train ng status and name of institut on
Subscriptions mav begin t a v time
Second class postage paid at St Louis Mo and additional ma ling offices

continued on



280
240
200
160
120
80
60
40
20
0
290
250
210
190
170
130
90
70
50
30
10







(Information for authors on page 17)

(Index to advertisers on page 42)

March 1980

American Heart Journal

Copyright © 1980 by The C V Mosby Company

Contents

continued on page

Vol. 99 No 3 March, 1980 The American Heart Journal is published monthly by The C V Mosby Company 11830 Westline Industrial Drive St Louis, Mo 63141

Annual subscription rates

	U.S	All foreign countries
Institutional	$45 00	$55 00
Personal†	$_8 00	$38 00
Student resident†	$22 40	$32 40

Single copies are $4.50 postpaid Remittances should be mad by check, draft, post office or express money order payable to this Journal.

Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals and clinics city county state provincial and national government bureaus and d partments and all commercial and pri ate institutions and org nizations.
†Personal subscriptions and all student rate subscriptions must be in the n mes of billed to and paid by individuals. All student rate requests must indicate training status and name of institution
Subscriptions may begin at any time
Second class postage paid at St Louis Mo and additional mailing offices.

r"cardiac separation"...

Although over 80% of post coronary patients can resume normal marital sexual activity *fear of anginal pain often results* in cardiac separation between patients and their families

You can help minimize cardiac *separation* with a program of counseling and often with a prescription for Cardilate (erythrityl tetranitrate)

Cardilate increases exercise tolerance helps patients return to more normal levels of activity—including sexual activity

Sublingually Cardilate begins to work within 5 minutes, eliminating or reducing frequency and severity of anginal pain for up to 2 hours

counsel & Cardilate®

(erythrityl tetranitrate)

CARDILATE® (ER THR T TETRA TR TE

INDICATIONS Car iat (E y y Tetra itr e is intended for he p ophyla is and long-term treatment of patient with frequent or recurrent anginal pa ... nitroglycerin

CONTRAINDICATIONS ... to th drug

WARNING Data supporting the use of ... during the early days of the ... period during which cl ... and ... insufficient ...

PRECAUTIONS ... glaucoma Tolerance to this drug and cross tolerance to other n ... may occur

ADVERSE REACTIONS ... headache is common ... may be severe and persistent Transient episodes of dizziness and weakness ... postural hypotension may occasionally develop ...

tion and collapse ... the usual therapeutic dose Alcohol may enhance the effect ...

DOSAGE AND ADMINISTRATION

... may be administered ... sublingual ... prior to ... physical or emotional stress ... The dose may be increased or decreased as needed

HOW SUPPLIED

CARDILATE ... BLE S scored ...

Burroughs Wellcome Co

Research Triangle Park North Carolina 27709



Contents *continued*

Hal Fisher is out for his morning ECG.

ıck's ambulatory ECG for patients on the go

Jogging cycling tennis Working out or *work routine* Most patient activities can be continued while you monitor his ECG This compact ambulatory monitor tells *you* what you need to know, detects ac events in the patient has known or suspected cardiac rmalities wherever he is Yet tunzed monitor/recorder weighs ɔunces and can be worn in a pocket ʾɜ shoulder or on the hip giving tient *complete* freedom of activity

lakes sense for the physician too cks ambulatory monitor offers many ad ges for the physician For *example* you hoose from a broad range of *automatic* ion and interval settings to achieve ECG oring programs from 15 hours to a week in ength And if the patient feels unusual symp- he can verbally record on tape his own feelings *on the spot* and activate a recording of his electrocardiogram This is selective monitoring at its best.

Simple playback Burdicks ambulatory *monitor enables you to play back the* recorded ECG directly into any standard office ECG unit *No* expensive scanning or data processing equipment *is needed*

Use for monitoring transient cardiac abnormalities or rehabilitation progress Ideally suited for determining the causes of transient *cardiac abnormalities* such as angina dyspnea dizziness *cerebral ischemia and for* monitoring cardiac rehabilitation progress

Seeing is believing For more information or a demonstration call us toll free at 800-356-0701 In Wisconsin call 608 868-7631 Or write **The Burdick Corporation, Milton, Wisconsin 53563**

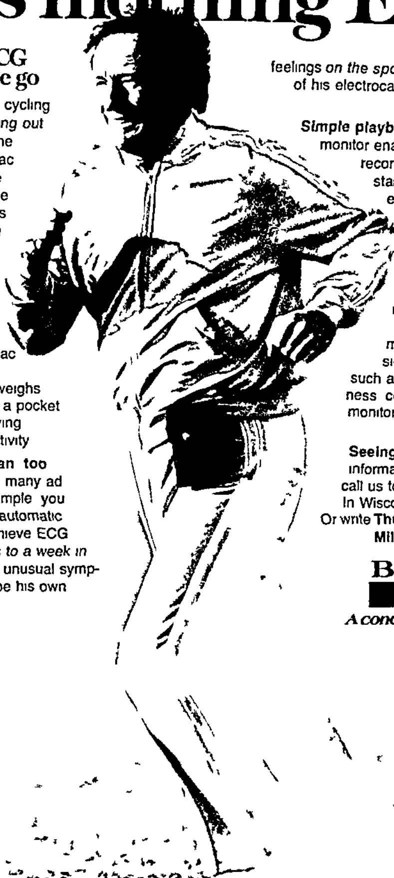
BURDICK

A concern for cardiac care.

Contents *continued*

(Information for authors on page 17)
(Index to advertisers on page 58)

Hal Fisher is out for his morning ECG.



ıck's ambulatory ECG for patients on the go

Jogging cycling *tennis Working out* or work routine Most patient ac tivities can be continued while you monitor his ECG *This com* pact ambula tory monitor tells you what you need to know detects ac *events in the patient* ıas known or suspected cardiac alities wherever he is Yet aturized monitor/recorder weighs ounces and can be worn in a pocket ıe shoulder or on the hip giving atient complete freedom of activity

akes sense for the physician too ck s ambulatory monitor offers many ad ges for the physician For example you hoose from a broad range of automatic on and interval settings to achieve ECG *oring programs from 15 hours to a week in* ength And if the patient feels unusual symp- he can verbally record on tape his own feelings *on the spot* and activate a recordir of his electrocardiogram This is selecti monitoring at its bes

Simple playback Burdick s ambulatoı monitor enables you to play back tł recorded ECG directly into ar standard office ECG unit N expensive scanning or da processing equipmeı is neede

Use for monitorin transient cardia abnormalities (rehabilitation progres Ideally suited for dete mining the causes of traı sient cardiac abnormalitie such as angina dyspnea dizı ness cerebral ischemia and fı monitoring cardiac rehabilitatio progres

Seeing is believing For mor information or a demonstratior call us toll free at 800-356 0701 In Wisconsin call 608 868 7631 Or write **The Burdick Corporation Milton, Wisconsin 53563**

BURDICK

A concern for cardiac care

April 1980

American Heart Journal

Copyright © 1980 by The C. V. Mosby Company

Contents

continued on page [illegible]

Vol. 99, No. 4, April 1980. The American Heart Journal is published monthly by The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Mo. 63141.

Annual subscription rates

	U.S.	*All foreign countries*
Institutional*	$45.00	[illegible]
Personal†	$29.00	$38.00
Student, resident†	$22.40	$32.40

Single copies are $4.50 postpaid. Remittances should be made by check, draft, post office or express money order, payable to this Journal.

*Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals and clinics, city, county, state, provincial and national government bureaus and departments, and all commercial and private institutions and organizations.
†Personal subscriptions and all student rate subscriptions must be in the names of, billed to, and paid by individuals. All student rate requests must indicate training status and name of institution.
Subscriptions may begin at any time.
Second class postage paid at St. Louis, Mo., and additional mailing offices.

is is tation

...

This is Station 7 at Memorial City General Hospital in Houston Texas where Abbott s new ACS Arrhythmia Central is helping unit staff in the anticipation and prevention of life-threatening cardiac events

While Station 7 is a general medical floor many of the unit s patients are graduates of the Critical Care Unit since many arrhythmias begin recurring days after a patient appears stable Others monitored by the ACS are Post Op or persons with suspected coronary problems who are not ill enough to be considered as CCU candidates

In all cases the 8-bed telemetry system watches for and trends arrhythmias that can foretell a possible impending crisis Treatment and drugs can be prescribed to reverse an arrhythmia pattern and block its recurrence

The concept is working at Memorial City General And Abbott s new ACS brings sophisticated and effective arrhythmia detection within practical reach of all hospitals regardless of size

More detailed information is available free from
Abbott Medical Electronics
8330 Broadway
P O Box 12696
Houston Texas 77017



Station 7 patients are monitored by means of battery powered telemetry transmitters Arrhythmias are more likely to occur with mobile rather than supine patients



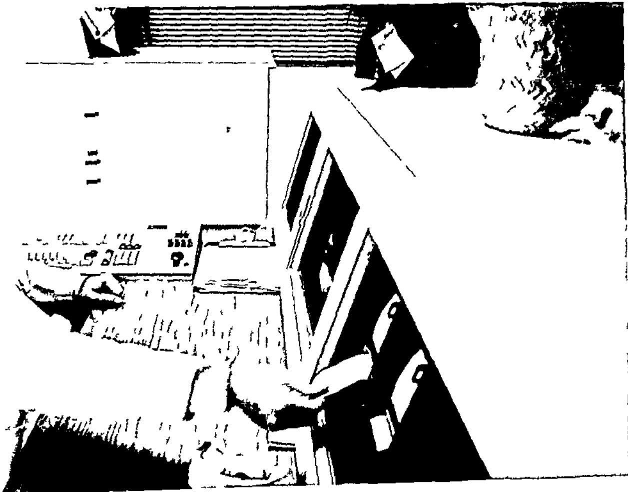
Ability to edit arrhythmia criteria if desired is a valuable feature of Abbott s ACS Operator/System communication is via keyboard



ABBOTT
Medical Electro ic

(Information for authors on page 17)

(Index to advertisers on page 52)



is

This is Station 7 at Memorial City General Hospital in Houston Texas where Abbott s new ACS Arrhythmia Central is helping unit staff in the anticipation and prevention of life-threatening cardiac events

While Station 7 is a general medical floor many of the unit s patients are graduates of the Critical Care Unit since many arrhythmias begin recurring days after a patient appears stable Others monitored by the ACS are Post Op or persons with suspected coronary problems who are not ill enough to be considered as CCU candidates

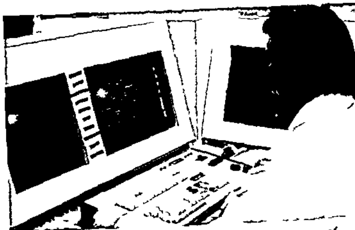
In all cases the 8-bed telemetry system watches for and trends arrhythmias that can foretell a possible impending crisis Treatment and drugs can be prescribed to reverse an arrhythmia pattern and block its recurrence

The concept is working at Memorial City General And Abbott s new ACS brings sophisticated and effective arrhythmia detection within practical reach of all hospitals regardless of size

More detailed information is available free from
Abbott Medical Electronics
8330 Broadway
P O Box 12696
Houston Texas 77017



Station 7 patients are monitored by means of battery powered telemetry transmitters Arrhythmias are more likely to occur with mobile rather than supine patients



Ability to edit arrhythmia criteria if desired is a valuable feature of Abbott s ACS Operator/System communication is via keyboard



ABBOTT
Medical Electronics

Contents *continued*

(Information for authors on page 17)

(Index to advertisers on page 52)

American Heart Journal

Contents

continued on page 7

Vol. 99 No 5 May 1980 The American Heart Journal is published monthly by The C. V Mosby Company 11830 Westline Industrial Drive St. Louis Mo 63141

Annual subscription rates

	U.S	All foreign countrie
Institutional	$45 00	$55 00
Personal†	$.8 00	$.8 00
Stud nt, resident†	$?? 40	$32.40

Single cop es are $4 50 postpaid Remittances should be made by check, draft post office or express money order payable to this Journal

Instit tional (multipl reader) subscript ons are a ailable to public and pri ate libraries schools, hospitals, and clinics city county st te provincial nd n tion l go ernment bureaus and departments and all commerc l and pri ate institut ons nd organizati ns.
†Person l subscriptions and all stud nt r te subscriptions must be in the n mes of billed to, and paid by individ ls All student rate requests must indicate traini g status and name of institution
Subscription may begin at any time
Second class postage paid at St. Lo is Mo and additional mailing offices.

or "cardiac separation"...

Although over 80% of post coronary patients can resume normal marital sexual activity, fear of anginal pain often results in cardiac separation between patients and their families

You can help minimize cardiac separation with a program of counseling and often with a prescription for Cardilate (erythrityl tetranitrate)

Cardilate increases exercise tolerance helps patients return to more normal levels of activity—including sexual activity

Sublingually Cardilate begins to work within 5 minutes eliminating or reducing frequency and severity of anginal pain for up to 2 hours

counsel & Cardilate®

(erythrityl tetranitrate)

CARDILATE® [illegible]

INDICATIONS [illegible] for the prophylaxis and long-term [illegible] of patients with frequent or recurrent anginal pain and reduced exercise tolerance associated with angina pectoris [illegible] some [illegible] that of nitroglycerin

CONTRAINDICATIONS [illegible]

WARNING Data supporting the use of [illegible] phase of myocardial infarction [illegible] period during which clinical and laboratory [illegible] are insufficient to establish safety

PRECAUTIONS Intraocular pressure is increased [illegible] to patients with glaucoma. Tolerance to this drug and cross tolerance [illegible] other nitrites and nitrates may occur

ADVERSE REACTIONS [illegible] is common and may be severe and persistent. Transient episodes of dizziness and [illegible] other signs of cerebral ischemia [illegible] may occasionally develop. This [illegible] antagonist [illegible] acetylcholine, histamine and many other agents. An [illegible] hypotensive effect [illegible] weakness [illegible] tion and collapse [illegible] occur even [illegible] the usual therapeutic dose. Alcohol may enhance this effect. Drug [illegible] may occasionally [illegible]

DOSAGE AND ADMINISTRATION
Oral [illegible] may be administered either sublingually [illegible] therapy may be initiated with 10 mg [illegible] each anticipated physical or emotional stress and [illegible] for patients subject to nocturnal attacks. The dose may be increased or decreased as needed

HOW SUPPLIED
CARDILATE [illegible] TABLETS Scored [illegible] 5 mg Bottle of 100 [illegible] Bottles of 100 and 1000 [illegible] Bottle of 100

[illegible] Sexual activity and the post coronary patient [illegible]

Burroughs Wellcome Co
Research Triangle Park North Carolina 27709



Contents *continued*

Contents *continued*

(Information for authors on page 17)
(Index to advertisers on page 62)

June 1980

American Heart Journal

Copyright © 1980 by The C V Mosby Company

Contents

continued on page 7

Vol. 99 No 6, June 1980 The American Heart Journal is published monthly by The C. V Mosby Company 11830 Westline Industrial Drive St. Louis Mo 63141

Annual subscription rates

	U.S	All foreign countries
Institutional	$45 00	$55 00
Personal†	$28.00	$38 00
Student resident†	$22.40	$32.40

Single copies are $4 50 postpaid. Remittances should be made by check, draft, post office or express money order payable to this Journal.

Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics city county state provincial and national government bureaus and departments and all commercial and private institutions and organizations.
†Personal subscriptions and all student rate subscriptions must be in the names of billed to and paid by individuals. All student rate requests must indicate training status and name of institution.
Subscriptions may begin at any time
Second class postage paid at St. Louis, Mo and additional mailing offices.

continued on page 9

Contents *continued*

(Information for authors on page 17)

(Index to advertisers on page 56)

American Heart Journal

January 1980 Volume 99 Number 1

Editorial

Brain peptides and pain sensation

W J Jeffcoate MA MRCP
London England

Auntie did you feel no pain
Falling from that apple tree?
Would you do it please again?
Cos my friend here didn t see
Harry Graham (1874 1936)

In certain circumstances extensive physical injuries can be sustained and yet give rise to no immediate pain The explanation remained obscure until very recently when the discovery of the enkephalins and the endorphins led to exciting speculation concerning the role of endogenous morphine like substances[1] Thus it seems that a number of these opioid peptides occur in the brain cerebrospinal fluid pituitary and plasma and that they are released by stress and other stimuli to induce analgesia It has been suggested also that their release mediates the analgesia induced by acupuncture and that alteration in levels of endogenous opioid peptides may underlie certain psychiatric diseases While such theories are undoubtedly fascinating they are by no means proven

Endogenous opioid peptides

The first substances with morphine like properties to be isolated from brain were two closely related pentapeptides methionine and leucine enkephalin The observation that methionine enkephalin represented a small fragment of the 9[…] aminoacid pituitary hormone β lipotropi[…] (β LPH) led to other fragments of the hormon[…] being studied Four such fragments (α β γ an[…] δ endorphin) were found to have morphine lik[…] activity β endorphin being the most potent

The parent molecule β LPH was first isolate[…] in 1964 by Dr C H Li and colleagues but afte[…] early theories concerning a possible role in th[…] control of fat metabolism had been discarded […] remained a peptide of no known function Howev[…] er it is thought to be formed by enzymati[…] cleavage from the same precursor molecule a[…] adrenocorticotropin (ACTH) and large molec[…] ular weight precursors have been identified[…] β LPH and ACTH are found in the same cells o[…] the pituitary gland and the two are release[…] together both basally and in times of stress[…] Therefore the discovery that fragments of β LP[…] possessed morphine like activity (even thoug[…] β LPH itself does not) seemed to make teleologi[…] cal sense endogenous opioid peptides wer[…] derived from a pituitary stress hormone an[…] would be available at times when painful injurie[…] are likely to be sustained

Measurement of endogenous opioid peptides

The enkephalins and endorphins unlike β[…] LPH share the ability to bind to opiate recepto[…] in animal tissue such as those on rat bra[…] synaptosomes mouse vas deferens and guinea p[…] ileum As this binding is stereospecific and […] competitively reversed by the morphine antago[…] nist naloxone it has been used as the basis of[…]

From th Departm nt of Endocrinology St Barthol mew s Hospital, Lond n England

Received fo publication J n 25 1979

Reprint requests Dr W J Jeff ate City Hospital N ttingham NG5 1PD Engl nd.

number of *in vitro* bioassays Unfortunately these assays do not differentiate between individual opioid peptides Specific radioimmunoassays for methionine and leucine enkephalins are now becoming available but it has not yet been possible to identify enkephalins circulating in either animal or human plasma

The measurement of the endorphins by specific radioimmunoassay poses special problems For theoretical reasons antisera developed to β endorphin will almost always cross react with the enkephalins the other endorphins or with the parent molecule β LPH This lack of specificity means that extreme care is necessary for the interpretation of levels of apparent β endorphin immunoreactivity in various animal fluids At the moment it is necessary to incorporate at least one chromatographic stage for the positive identification of any of the endorphins less exacting data merely provide suggestive evidence

Are opioid peptides concerned with endogenous analgesia?

There is a mass of highly suggestive circumstantial evidence to implicate the involvement of an opioid pathway in endogenous analgesic mechanisms although most of this evidence is derived from study of morphine antagonists Thus naloxone has been shown to lower the resting pain threshold in both mice and men and to reverse the analgesic effect of hypnosis and placebo Moreover the profound analgesia which is induced by electrical stimulation of the periaqueductal grey matter is also partially reversed by the administration of a morphine antagonist In addition Akil and colleagues have recently shown that in humans analgesia achieved by stimulation of the periaqueductal grey matter is associated with a rise in enkephalin like material in cerebrospinal fluid

Further support comes from immunofluorescent studies which have been performed to localize the enkephalins and endorphins in different tissues Although the peptides are found in most parts of the central nervous system as well as in the anterior and intermediate lobes of the pituitary gland they are present in particularly high concentration in those areas thought to be associated with modification of pain sensation the substantia gelatinosa of the dorsal horns in the spinal cord and the periaqueductal grey matter of the brain stem

Unsolved problems

It seems likely that with the development of more sensitive and specific techniques for the assay of the enkephalins and the endorphins these peptides will be shown to play a major role in the modification of pain sensation Moreover such techniques will help solve some of the problems that have been encountered

A Relationship between β LPH and opioid peptides in pituitary and brain Data currently available have failed to establish any relationship between the levels of apparent endorphin or enkephalin in CSF brain and plasma Patients with hypopituitarism have normal levels of immunoreactive β-endorphin in CSF and hypophysectomy has no effect on the brain content of opioid peptides in experimental animals If it is true that opioid peptides present in brain are not derived from the pituitary the significance of β LPH being a stress hormone is lost and indeed β LPH becomes once more a pituitary peptide of unknown function Moreover β LPH is related structurally only to methionine-enkephalin and there is no equivalent parent molecule for leucine enkephalin

B Why are there so many opioid peptides? As all of the enkephalins and endorphins have qualitatively similar actions there is no apparent reason for their separate existence While it may be that β endorphin is the major opioid peptide and that the other endorphins together with methionine enkephalin merely represent different stages of its metabolism it seems more likely that a discrete role will be found for each of these substances In particular the distribution of the enkephalins in nerve terminals and the existence of pathways for their rapid breakdown suggest that they act as neurotransmitters On the other hand the endorphins are comparatively stable in body fluids and they may well act as neuromodulators rather than transmitters

Whatever the physiological action of these substances is finally shown to be their discovery has reawakened interest in the study of opiate drugs It is to be hoped that such work will lead to greater understanding of the way in which these drugs act and eventually will lead to the development of more effective means of controlling pain

I thank Professor Lesley Rees and Professor Michael Besser for their advice and support

EFERENCES

1 Hughes, J Smith T W Kosterlitz H W, Forthergill L A Morgan B A and Morris, H R Identification of two related pentapeptides from the brain with potent opiate agonist activity Nature 258 577 1975
2 Bradbury A F Smyth D G and Snell C R in Peptides Chemistry Structure and Biology Ed R Walter and J Meienhofer Ann Arbor 1975 Ann Arbor Sci. Inc p 609
3 Li C H and Chung D Isolation and structure of an untriakontapeptide with opiate activity from camel pituitary glands Proc Natl Acad. Sci. USA 73 1145 1976
4 Leading Article Human beta endorphin the real opium of the people? Br Med J 2 155 1978
5 Leading Article Enkephalins the search for a functional role Lancet 2 819 1978
6 Byck R Peptide transmitters A unifying hypothesis for euphoria respiration sleep and the action of lithium Lancet 2 72 1976
7 Jacquet Y F and Marks, N The C fragment of β lipotropin An endogenous neuroleptic or antipsychotogen? Science 194 632 1976
8 Van Ree J M., De Wied D Bradbury A F Hulme E C Smyth D G and Snell, C R Induction of tolerance to the analgesic action of lipotropin C fragment Nature 264 792 1976
9 Bloom F Segal D Ling N and Guillemin R Endorphins Profound behavioural effects in rats suggest new etiological factors in mental illness Science 194 630 1976
10 Guillemin R Endorphins, brain peptides that are like opiates N Engl J Med 296 226 1977
11 Birk Y and Li, C H Isolation and properties of a new biologically active peptide from sheep pituitary glands J Biol Chem 239 1048 1964
12 Lowry P J Silman R E Hope J and Scott, A P Structure and biosynthesis of peptides related to corticotropins and β melanotropins Ann N Y Acad Sci. 297 49 1977
13 Mains, R E Eipper B A and Ling N Common precursor to corticotropins and endorphins Proc Natl Acad Sci. USA 74 3014 1977
14 Pelletier G Leclerc R Labrie F Cote J Chretien M and Lis M Immunohistochemical localisation of β lipotropic hormone in the pituitary gland Endocrinology 100 770 1977
15 Jeffcoate W J Rees Lesley H Lowry P J and Besser G M A specific radioimmunosasay for human β lipotropin J Clin Endocrinol. Metab 47 160 1978
16 Paton W D M and Vizi E S The inhibitory action of noradrenaline and adrenaline on acetylcholine output by guinea pig ileum longitudinal muscle strip Br J Pharmacol. 35 10 1969
17 Henderson G., Hughes J., and Kosterlitz H W A new example of a morphine sensitive neuro-effector junction adrenergic transmission in the mouse vas deferens, Br J Pharmacol 46 764 1972
18 Lord J A H., Waterfield A A., Hughes J and Kosterlitz H W Endogenous opioid peptides multiple agonists and receptors Nature 267 495 1977
19 Yang H Y Hong J S and Costa E Regional distribution of leu and metenkephalin in rat brain Neuropharmacol 16 303 19 7
20 Akil H Watson S J Sullivan S and Barchas J D Enkephalin like material in normal human CSF measurements and levels, Life Sci. 23 121 1978
21 Frederickson R C A Burgis V., and Edwards, J D Hyperalgesia induced by naloxone follows diurnal rhythm in responsivity to painful stimuli, Science 198 756 1977
22 Lasagna L Drug interaction the field of analgesic drugs Proc R Soc Med 58 978 1965
23 Stephenson J B P Reversal of hypnosis-induced hyperalgesia by naloxone Lancet 2 991 1978
24 Levine J D Gordon N C and Fields H L The mechanism of placebo analgesia Lancet 2 654 1978
25 Adams J E Naloxone reversal of analgesia produced by brain stimulation in the human Pain 2 161 19 6
26 Mayer D J and Hayes R L Stimulation produced analgesia development of tolerance and cross tolerance with morphine Science 188 941 1975
27 Akil, H., Mayer D J and Liebeskind J C Antagonism of stimulation produced analgesia by naloxone a narcotic antagonist Science 191 961 19 6
28 Akil H Richardson D E., Hughes J and Barchas J D Enkephalin like material elevated in ventricular cerebrospinal fluid of pain patients after analgetic focal stimulation Science 201 463 1978
29 Jeffcoate W J Rees L., McLoughlin L. Ratter S J Hope J Lowry P J and Besser G M β-endorphin in human cerebrospinal fluid Lancet 2 119 1978
30 Cheung A L and Goldstein A Failure of hypophysectomy to alter brain content of opioid peptides (endorphins) Life Sci. 19 1005 1976
31 Neale J H., Barker J L Uhl G R., and Snyder S H Enkephalin containing neurones visualised in spinal cord cell cultures, Science 201 467 19 8
32 Hughes J Isolation of an endogenous compound from the brain with pharmacological properties similar to morphine Brain Res 88 295 1975

Clinical setting and prognostic significance of high degree atrioventricular block in acute inferior myocardial infarction a study of 144 patients

Alfred C Tans M D *
K I Lie M D
Dirk Durrer M D
Amsterdam The Netherlands

Atrioventricular (AV) block has been reported in 12 to 25% of patients with acute myocardial infarction [1-3] All forms of AV block occur two to four times more frequently in acute inferior myocardial infarction (IMI) as compared to anterior myocardial infarction The conduction disturbances during acute IMI are usually located in the AV node [1,2] presumably due to occlusion proximal to the origin of the AV nodal artery the latter is in 90% of cases a branch of the right coronary artery [4]

It has been proposed that indications for pacemaker therapy in AV block complicating acute IMI are Stokes Adams attacks power failure (congestive heart failure or shock) and bradycardia dependent ventricular arrhythmias How ever in the subgroup with power failure it is unclear and controversial as to whether pacemaker therapy influences immediate prognosis [5]

This study therefore evaluates the clinical setting and prognostic significance of high degree AV block in acute IMI as well as the therapeutic value of pacing From these data we will try to outline more precisely indications for pacemaker therapy

From th Department of Card ology and Cl n al Physiology Univer sity of Amsterdam Wilhelmina Ga thuis and Interunivers ty Cardiol ogy Institute Amsterdam The Neth rlands

Received for publication May 15 1979

Accepted for publication July 16, 1979

Present address and reprint requests Alfred C Tans M D D pt of Card ology Slotervaart Ziekenhuis Louwesweg 6, 106C EC Am ter dam The Netherlands

Material and methods

The subjects were patients admitted to the coronary care unit because of acute IMI

The diagnosis of acute infarction was based on a typical history of chest pain correlated with the appearance of diagnostic Q waves and character istic serial changes in serum enzymes In all patients continuous electrocardiographic moni toring was performed The location of infarction was defined according to the criteria of the New York Heart Association [6] IMI included diaphrag matic and/or posterior infarction with or with out lateral involvement Patients with both ante rior or anteroseptal and inferior infarction were excluded from the study High degree AV block was defined as the presence of second degree AV block occurring via a type I mechanism two to one block atrial fibrillation with a ventricular rate of less than 60/minute provided that the patient did not use digitalis and third degree AV block

In third degree AV block the atrial rate was always considerably higher than the ventricular rate

Only those patients were included in the study in whom the AV block lasted for at least half an hour The presence and degree of power failure at the time of onset during and following the episode of high degree AV block were noted Severe power failure was defined as shock (a systolic blood pressure of less than 90 mm H peripheral vascular constriction and an altered sensorium) Shock was considered irreversible

0002 8703/80/010004 + 05$00 50/0 © 1980 The C V Mosby Co

Table I Incidence age sex mean peak SGOT and mortality rate

	All pts with IMI	*Pts without high degree AV block*	*Pts with high degree AV block*
No	843	699	144
Mean age (yr)	63	62	65
Sex			
male	627	517	110
female	216	182	34
Mean peak SGOT (I U)	100	92	140
Mortality rate (%)	12	9	22

when it persisted despite appropriate therapy including pacing

The significance of differences between mean ages and mean peak values for SGOT were tested with Student s t test A chi square test was used to test the significance of differences in incidence

Results

Incidence and mortality rate In a period of 5 years (1972 to 1976) 843 patients were admitted to the coronary care unit because of acute IMI Of these 144 (17%) had high degree AV block (Table I) The mean age of the patients with high degree AV block was higher (65 years) than that (62 years) of those without high degree AV block ($p < 0.01$) The mean peak SGOT was significantly higher ($p < 0.001$) in the patients with high degree AV block (140 I U) than in those without AV block (92 I U) The hospital mortality rate of patients with acute IMI complicated by high degree AV block was significantly higher of the 144 patients 32 died (22%) compared to 65 (9%) of the 699 patients without high degree AV block ($p < 0.001$) This difference was even significant if both subgroups were matched for age

The cause of death in the patients with AV block was primarily power failure of the 32 patients 18 died of cardiogenic shock and six of congestive heart failure Five patients died of cardiac rupture In two patients the cause was non cardiac and in one it was unknown

Electrocardiographic course of high degree AV block The maximal degree of AV block did not influence the immediate prognosis 12 of 50

Table II ECG prior to and following second degree AV block

		No			*Totals*
1 ——→	2	59	91	→ 3	41
Normal PR →	2	7		→ 1	43
On admission	2	25		→ †	7

1 = first-degree AV block = second-degree AV block 3 = third degree AV block
† = death during second-degree AV block
PR = PR interval

Table III ECG prior to and following third degree AV block

		No			*Totals*
1 → 2 →	3	24	94	→ 2 → 1	60
2 →	3	17			
Normal PR →	3	9		→ 1	24
On admission	3	44		→ †	10

1 = first-degree AV block 2 = second-degree AV block 3 = third degree AV block
† = death during third-degree AV block
PR = PR interval

patients (24%) with second degree AV block only died compared to 20 of 94 (21%) with third-degree AV block Second-degree AV block was registered in 91 patients (Table II) In 59 of these first degree AV block was noticed prior to the onset of second degree AV block while in the 32 others it was the first manifestation of the AV conduction disturbance in the coronary care unit In 41 patients (45%) the conduction disturbance progressed into third degree AV block Seven patients died during second degree AV block and five others died after returning to 1 1 AV conduction

Ninety four patients demonstrated third degree AV block (Table III) As mentioned 41 patients progressed from first and /or second degree to third-degree AV block while 53 patients manifested it as their initial conduction disturbance Eighty four patients returned to 1 1 AV conduction either through a phase of second degree AV block (60) or directly (24) Ten patients died during third degree AV block while ten others died after returning to 1 1 AV conduction All survivors of high degree AV block were discharged from the hospital with 1 1 AV conduction

Table IV Escape frequency during third degree AV block

Beats /min.	No		Mortality (No)		PM (No)	
≤ 30	8	74	4	14	7	60
31-40	34		6		26	
41-50	32		4		27	
51-60	1	20	5	6	9	11
61-70	3		1		1	
> 70	2		0		1	

PM = temporary pacemaker therapy

Table V Management of high degree AV block

	No	Mortality	
		No	%
PM	85	18	21
None or Atropine	59	14	24
Total	144	32	22

P.M = temporary pacemaker therapy

Time of onset of high degree AV block In almost half of the patients (69 of 144) the high degree AV block was already present on admission In only five of these 69 was the delay between onset of symptoms of IMI and admission longer than 24 hours Of the 44 patients with third-degree AV block on admission 27 had a Stokes Adams attack and/or syncope prior to admission High degree AV block had developed within 24 hours after onset of symptoms in 69% and within 3 days in 92% of the patients The latest observed onset of high degree AV block was on the fifth day of IMI The *duration* of high degree AV block varied from half an hour to 16 days It was less than 24 hours in 37% and more than 3 days in 47% of the patients

Width of the QRS complexes during third degree AV block An escape rhythm with widened (more than 0 12 sec) QRS complexes was observed in 35 of the 94 patients (37%) They all had narrow QRS complexes in the conducted beats These widened QRS complexes had a left bundle branch block configuration in seven patients, a right bundle branch block configuration in 21 and both LBBB and RBBB in seven patients The mechanisms of these widened QRS complexes have been described before[2]

Escape frequency during third-degree AV block Mortality was not influenced by the rate of the escape pacemaker at the time of onset of AV block being 19% (14 of 74) when the rate was ≤ 50/minute and 30% (six of 20) when it was > 50/minute (N S) Sixty of the 74 patients (81%) with a frequency ≤ 50/minute were treated with a temporary pacemaker compared to 11 of the 20 patients (55%) with a frequency > 50/minute (Table IV)

Management Eighty five of the 144 patients with high degree AV block (59%) were temporarily paced (Table V) according to the indications listed before Of the 59 patients not paced eight were successfully treated with atropine whereas in the other 51 patients no treatment was necessary The mortality rate of the patients who were paced (21%) was not significantly different from that of the patients who were not paced (24%)

Hemodynamic condition and ventricular rate

Forty two of the 144 patients demonstrated shock either at the time of onset of the AV block or when the high degree AV block was already present on admission (Table VI) Thirty one of these 42 patients had a ventricular rate of 50 per minute or less Eleven of these 31 patients were initially treated with atropine with only one improving One patient improved without treatment Twenty nine of these 31 patients were treated with a temporary pacemaker and the shock was found to be reversible in 24 with only one late death The remaining five patients did not respond to pacemaker therapy and died in irreversible shock

Eleven of the 42 patients in shock had a ventricular rate of more than 50 per minute and six were paced Three of these six showed initial improvement of their hemodynamic condition with only one late death The other three did not respond to pacemaker therapy and died in irreversible shock The remaining five patients were not paced because four had second-degree AV block only with a ventricular rate of 80 per minute or more and one refused pacemaker insertion all five died in irreversible shock. Of the 102 patients who were not in shock at the time of onset of high degree AV block 17 died

A Stokes Adams attack and /or syncope prior to admission occurred in 22 of the 31 patients (71%) with initial shock and a ventricular rate of less than 50 beats per minute in three of the 11 patients (27%) with shock and a ventricular rate

Table VI Hemodynamic condition and ventricular rate during high degree AV block

	Shock						No shock		
	VR ≤ 50/min			*VR > 50/min*					
		Mortality			*Mortality*			*Mortality*	
Management	*No*	*No*	*%*	*No*	*No*	*%*	*No*	*No*	*%*
PM	29	6	21	6	4	67	50	8	16
None or Atropine	2	0	0	5	5	100	52	9	17
Total	31	6	19	11	9	82	102	17	17

VR = ventricular rate PM = temporary pacemaker therapy
$p < 0.006$

of more than 50 beats per minute and in 19 of the 102 patients (19%) who were not in shock

Discussion

Patients with acute inferior myocardial infarction complicated by high degree AV block have a higher mortality rate than do those without high degree AV block (Table I) Also there is a high incidence of severe power failure especially at the time of the first manifestation of the high degree AV block in the coronary care unit There are two possible explanations for these findings Either the high degree AV block may only be a manifestation of an inferior infarction with more extensive myocardial damage as manifested by a higher mean peak SGOT or the conduction disturbance itself may contribute to the development of power failure extension of infarction and hence a higher mortality

In contrast to Rotman and associates[9] our data indicate that even patients with high degree AV block and no severe power failure had a higher mortality rate (17%) than did patients with IMI without high degree AV block (9% $p < 0.05$) In the subgroup with high degree AV block without severe power failure there was no difference in mortality rate between those who were paced (16%) and those who had an acceptable ventricular rate and did not need a temporary pacemaker (17%) (Table VI) We believe that in this group of patients without severe power failure the higher mortality rate is mainly due to more extensive myocardial damage and not to the AV block itself However there seems to be a subset of patients with high degree AV block in which the conduction disturbance contributes to the subsequent clinical course

The characteristics of these patients are severe power failure at the time of onset of the high degree AV block associated with a low ventricular rate

It appeared that in this group of patients with shock the ventricular rate was of prognostic significance (Table VI) 31 patients were in shock and had a ventricular rate of 50 per minute or less Most of these patients were paced and it was found that in the majority the shock was reversible soon after pacing was started The mortality rate in this group with initial shock and a low ventricular rate was 19% which is not significantly different from the mortality rate (17%) of the group without severe power failure However when the ventricular rate was more than 50 per minute most of the patients with shock did not respond to treatment and died in irreversible shock In these patients pacemaker therapy seems not to affect the immediate prognosis We believe that in patients presenting with both high degree AV block and shock it is not possible to distinguish between irreversible shock secondary to massive myocardial damage and reversible shock caused by both extensive myocardial damage and the conduction disturbance itself The latter situation seems to occur especially in patients with shock and a low ventricular rate We are aware that we as well as others[9, 11] do not have hard data to establish this statement but it is in our view unethical to determine the true natural history of symptomatic high degree AV block complicating acute IMI by withholding pacemaker therapy in such patients

A possible reason for the high incidence of reversible shock that cannot be ruled out in our patients is right ventricular infarction Right

ventricular involvement in IMI is reported to occur in 40% of cases[1] with hemodynamic alterations such as a lowered right ventricular ejection fraction[13] Recently Lorell and colleagues reported that temporary pacing did not alleviate hypotension in patients with IMI and a right ventricular infarction From 12 patients with IMI right ventricular infarction and arterial hypotension nine needed temporary pacing but in none was hypotension corrected by pacing alone In contrast our patients with reversible shock did show improvement of the hemodynamic condition soon after pacing (the only therapy) was started

Therefore we believe that more data are necessary to evaluate the effect of cardiac pacing on both right and left ventricular function in patients with high degree AV block complicating acute IMI who are either symptomatic or have a low ventricular rate

Summary

High degree AV block occurred in 144 of 843 patients consecutively admitted because of acute inferior myocardial infarction and was associated with more extensive myocardial damage and a higher mortality rate as compared to those without AV block

Patients with power failure at the time of appearance of high degree AV block and a ventricular rate of less than 50 per minute seemed to profit from pacemaker therapy

By contrast in patients with power failure and a ventricular rate of more than 50 per minute pacemaker insertion did not affect immediate prognosis

REFERENCES

1 Norris, R M and Mercer C J Significance of idioventricular rhythms in acute myocardial infarction Progr Cardiovasc Dis 16 455 19 4
2. Resnekov L and Lipp H Pacemaking and acute myocardial infarction Progr Cardiovasc Dis 14 4 5 19 2
3 Rotman M Wagner G S and Wallace A G., Bradyarrhythmias in acute myocardial infarction Circulation 45 03 19 2
4 Bigger J T., Dresdale R J., Heissenbuttel R H., Weld F M., and Wit A L. Ventricular arrhythmias in ischemic heart disease Mechanism prevalence significance and management Progr Cardiovasc Dis 19 255 19 7
5 Rosen K M Loeb H S., Chuquimia R., Zaid Sinno M Rahimtoola S H and Gunnar R M Site of heart block in acute inferior myocardial infarction Circulation 42 925 1970
6. James T N The coronary circulation and conduction system in acute myocardial infarction Progr Cardiovasc Dis 10 410 1968
7 Kostuk W J and Beanlands D S Complete heart block associated with acute myocardial infarction Am J Cardiol 26 380 1970
8 Rotman M Wagner G S and Waught R A Significance of high degree atrioventricular block in acute posterior myocardial infarction Circulation 47 257 1973
9 The Criteria Committee of the New York Heart Association Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels Boston 19 3 Little Brown & Company
10 Lie K I Wellens H J J Schuilenburg R M and Durrer D Mechanisms and significance of widened QRS complexes during complete atrioventricular block in acute inferior myocardial infarction Am J Cardiol 33 833 19 4
11 Friedberg C K Cohen H and Donoso E Advanced heart block as a complication of acute myocardial infarction Role of pacemaker therapy Progr Cardiovasc Dis 10 466 1968
12 Sharpe D N Botvinick E H Shames D M Schiller N B Massie B M Chatterjee K and Parmley W W The non invasive diagnosis of right ventricular infarction Circulation 57 483 1978
13 Tobinick E Schelbert H R Henning H Lewinter M Taylor A Ashburn W L and Karliner J S Right ventricular ejection fraction in patients with acute anterior and inferior myocardial infarction assessed by radionuclide angiography Circulation 57 1078 1978
14 Lorell B Leinbach R C Pohost G M., Gold H K., Dinsmore R E Hutter A M Pastore J O., and De Sanctis R W Right ventricular infarction Am J Cardiol 43 465 19 9

The heart in chronic alcoholism a noninvasive study

Alexander Askanas M D
Mallikarjun Udoshi M D
Seyed A Sadjadi M D
New York N Y

An association between chronic alcoholism and cardiac dysfunction has been studied and documented repeatedly Moreover some alcoholic subjects develop severe congestive heart failure presumably secondary to alcoholic cardiomyopathy[1,2]

It has been reported that acute administration of alcohol may also produce transient abnormality of cardiac function[3] Chronic alcoholic individuals without clinical evidence of heart disease may have abnormal systolic time intervals[4,5] The hearts of chronic alcoholic patients dying of non-cardiac causes show ventricular hypertrophy at autopsy

In the present investigation a noninvasive evaluation of the hearts of chronic alcoholic subjects without clinical evidence of heart disease was performed by combining an echocardiographic examination with the determination of systolic time intervals

The objective was to ascertain whether structural or functional cardiac abnormalities exist in alcoholic subjects without apparent evidence of heart disease

Material

Eighty five male chronic alcoholic subjects below the age of 45 years were studied In 73 of them high quality echocardiographic tracings were obtained and are the subject of this study (Group A = alcoholics)

The patients were admitted to the alcohol detoxification unit of the Hospital for Joint Diseases & Medical Center during the period of 1976 to 1978 and were studied between 3 and 6 days after admission All had been drinking an amount equivalent to at least 12 oz of whiskey daily for at least five years None had any history of heart or lung disease hypertension or diabetes Physical examination in all revealed normal blood pressure and no evidence of congestive heart failure Since sex difference has been reported in the effect of alcohol on the heart only males were examined[5] To decrease the probability of concomitant coronary artery diseases only patients below the age of 45 years were investigated

As a control group 30 carefully selected male hospital employees without any clinical evidence of or history of heart disease were studied (Group N = normal controls) All were below the age of 45 years None had high blood pressure and none drank more than small amounts of alcohol occasionally As a comparison group nine male alcoholic subjects with severe congestive heart failure were studied (Group C = alcoholics with congestive heart failure) All were also below the age of 45 years all were studied at the same time period and none presented either history or evidence suggesting valvular coronary or hypertensive cardiovascular disease They were presumably patients with alcoholic cardiomyopathy In two of those patients cardiac catheterization confirmed the diagnosis of congestive cardiomyopathy

From the Hospital for Joint Diseases and Medical Center New York N Y

Received for publication May 21 1979
Accepted for publication Aug 7 1979

Reprint requests Dr Alexander Askanas, Hospital for Joint Diseases and Medical Center 1919 Madison Ave New York N Y 10035
Present address Elmhurst Hospital Queens N Y

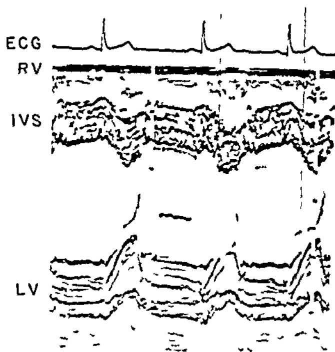


Fig 1 Echocardiogram of a chronic alcoholic patient revealing increased thickness of the interventricular septum (IVS) = 14 mm., and posterior wall of the left ventricle (LV) = 12 mm The myocardial contractility is normal ECG = electrocardiogram RV = right ventricle

Methods

Systolic time intervals were calculated from Lead II of the electrocardiogram and the phonocardiogram recorded at the left sternal border and carotid pulse tracing The tracings were recorded utilizing a VR 6 Electronics for Medicine recorder at a paper speed of 100 mm /sec Five complexes were measured and averaged (all patients were in sinus rhythm) The rate correction of left ventricular ejection time (LVET) was calculated according to the method of Weissler and associates[9]

Left ventricular ejection time (LVET) was measured from the upstroke of carotid pulse to the incisura Pre ejection period (PEP) was calculated as the difference between the Q A_2 interval and LVET The Q A_2 interval was measured from the beginning of the QRS complex to the first component of the second heart sound

Echocardiograms were obtained with a VR6 Electronics for Medicine recorder with an 0 5 inch 2 25 MHz transducer focused at 5 cm Echocardiograms were recorded with subjects in a slightly left lateral decubitus position After obtaining clear mitral echoes of both anterior and posterior leaflets the transducer was angled laterally and inferiorly to obtain clear septal and posterior wall endocardial echoes (Fig 1) The ventricular dimensions were measured at the level of the chordae tendineae All diastolic echocardiographic measurements were made at the beginning of the QRS complex according to the Committee on M Mode Standardization of the American Society of Echocardiography

The following formulae were used

Shortening Fraction (SF%)

$$\frac{Dd\ Ds}{Dd} \times 100 \text{ where} \tag{1}$$

Dd = diastolic dimension Ds = systolic dimension

Ejection Fraction (EF)

$$\frac{EDV\ ESV}{EDV} \text{ where} \tag{2}$$

EdV = end diastolic volume ESV = end systolic volume and SV = stroke volume

Cardiac volumes were calculated according to the Teicholtz correction[10]

$$V = D^3 \times \frac{7\ 0}{D + 2\ 4} \text{ where} \tag{3}$$

V = volume D = dimension

Mean velocity of circumferential fiber shortening (VCF[ci] /)[11]

$$\frac{Dd\ Ds}{Dd \times LVET} \text{ where} \tag{4}$$

LVET = left ventricular ejection time

Left ventricular mass (LV mass gm) was obtained by a modification of the method of Troy and colleagues[11 12]

$$1\ 05\ [(Dd + IVS + LV_s)^3\ Dd^3] \text{ where} \tag{5}$$

IVS_s = interventricular septum thickness and LV = left ventricular wall thickness

Normalized left ventricular posterior wall Velocity

(VpW cm /sec)[11]

Table I General evaluation and systolic time intervals in three groups*

Groups†	No	Age (yr)	BSA (M²)	Blood pressure (mm Hg) Syst	Diast	HR (min)	Years of drinking	PEP (Sec)	LVET (Sec)	LVETI (Sec)	PEP/LVET	C/T	SV₁ + RV₅ (mm)
A	73	34.4	1.77	117.[illegible]	77	76	15.2	0.106	0.[illegible]0	0.400	0.39[illegible]	0.45	3[illegible]
±S D		6.0	0.17	9.8	9.3	12	7.0	0.012	0.030	0.028	0.0[illegible]	0.043	8.9
N	30	32.4	1.84	117.7	76	76	–	0.09[illegible]	0.297	0.416	0.313	0.44	30.5
±S D		5.7	0.23	10.0	[illegible]	[illegible]		0.014	0.02[illegible]	0.0[illegible]4	0.0[illegible]1	0.037	9.4
C	9	36.1	1.68	117.6	78	98.3	1[illegible].1	0.131	0.205	0.3[illegible]2	0.6[illegible]0	0.61	29.4
±S D		6.2	0.13	11.8	6	12.8	5.0	0.017	0.029	0.021	0.116	0.04	11.5
p value													
A vs N		NS	NS	NS	NS	NS	–	<0.001	<0.001	<0.01	<0.001	NS	NS
N vs C		NS	NS	NS	NS	< 0.01	–	<0.001	<0.001	<0.001	<0.001	<0.001	NS
A vs C		NS	NS	NS	NS	< 0.01	NS	<0.001	<0.001	<0.01	<0.001	<0.001	NS

*Mean and standard deviation.
†A = alcoholics N = normal controls C = alcoholics with congestive heart failure BSA = body surface area HR = heart rate PEP = pre-ejection period LVET = left ventricular ejection time LVETI = left ventricular ejection time index C/T = cardiac thoracic ratio SV₁ + RV₅ = the sum of the amplitude of the S wave in Lead V₁ and R wave in Lead V₅

$$\frac{PWE}{LVET \times Dd} \text{ where} \qquad (6)$$

PWE = posterior wall excursion
Normalized interventricular septal velocity (Vivs cm/sec)[1]

$$\frac{IVSE}{LVET \times Dd} \text{ where} \qquad (7)$$

IVSE = interventricular septal excursion

All echocardiographic measurements were corrected for body surface area (BSA)

A detailed medical history physical examination 12 lead electrocardiogram and posteroanterior chest x ray were performed

The mean and standard deviation values were calculated and the data were subjected to Student's t test

Results

The non cardiac alcoholic subjects (Group A) did not differ from normal controls (Group N) in age body surface area heart rate blood pressure and cardiothoracic ratio (Table I)

Electrocardiogram There was no difference either in the voltage of QRS complexes or the incidence of ST T abnormalities between the normal subjects and non cardiac alcoholic subjects

The electrocardiograms of alcoholic patients with cardiomyopathy (Group C) were abnormal in all cases All patients had evidence of left atrial enlargement (except one patient with atrial fibrillation) Marked ST T abnormalities were present in all of them and left ventricular hypertrophy was present in seven out of nine

Systolic time intervals Both groups of alcoholic subjects cardiac and non cardiac had abnormal systolic time intervals Pre ejection period was prolonged Left ventricular ejection time was shortened and therefore PEP/LVET increased (Table I) These abnormalities were most marked in patients with congestive heart failure

Echocardiograms The echocardiograms of non cardiac alcoholic subjects (Group A) when compared with normal controls revealed highly significant thickening of the interventricular septum and the left ventricular wall as well as the increase of the left ventricular mass (p < 0.001) Table II)

Fifty two per cent of the patients in Group A (Fig 1) had markedly increased left ventricular mass (2 SD above the mean of the normal controls (Table III) Left ventricular thickness and interventricular septal thickness were

[1]Since BSA correction did not significantly change any of the data instead of presenting two sets of data (corrected and uncorrected) the echocardiographic measurements are presented in the uncorrected form only and the left ventricular volumes and mass are presented in the customary BSA corrected form.

Table II Echocardiographic data in three groups*

Group†	No	Dd (mm)	Ds (mm)	LA (mm)	IVSt (mm)	LVt (mm)	PWE (mm)	IVSE (mm)	SF (%)
A	73	49 5	31 1	29	11 71	10 4	11 5	8 1	37
± SD		›1	4 9	4 8	1 33	1 0›	2 2	2 (	6 5
N	30	47 ‿	30 4	28 3	9 63	8 76	11 7	7 7	35
± SD		4 3	4	4 3	1 ?4	0 86	2 3	2 1	4 5
C	9	66 9	›0	43	11 78	11 28	5 4	2 9	11 8
± SD		5 ?	? 2	6 (	1 6	1 39	2 (	1 0	3 0
p value									
A vs N		<0 0›	NS	NS	<0 001	<0 001	NS	NS	NS
N vs C		<0 001	<0 001	<0 001	<0 001	<0 001	<0 001	<0 001	<0 001
A vs C		<0 001	<0 001	<0 001	NS	<0 01	<0 001	<0 001	<0 001

Mean and standard deviation

†Abbreviations as in Table I Dd = diastolic dimension Ds = systolic dimension LA = left atrial dimension IVSt = interventricular septal thickne LVt = left ventricular thickness PWE = posterior wall excursion SF = shortening fraction VCF = velocity of mean circumferential fiber sh rtenin LVDV = left ventricular diastolic volume LVSV = left ventricular systolic volume SV = stroke volume EF = ejection fraction LV mass = le ventricular mass Vpw = normalized posterior wall velocity Vivs = normalized interventricular septal velocity IVSE = interventricular septal excu sion

The addition of I (Index) to abbreviation means body surface correction

Table III Incidence of abnormalities (above or below 2 SD from normal controls)

Group	PEI	LVETI	PEI / LVET	C/T	Dd	Ds	IVSt	LVt	LVDVI	LVSVI	LV mass I
A	10(13 7)	6(8 2)	16(?2)	6(8 ?)	10(13 7)	6(8 ?)	31(42 5)	34(46 6)	9(12 3)	15(20 5)	38(52)
N	0	0	0	1(3 3)	0	1(3 3)	0	0	1(3 3)	1(3 3)	1(3 3)

Number of subjects Percentage in parentheses.
Abbreviations as in Tables I and II

increased 2 SD above mean of normal control in 47% and 43% respectively (Table III)

There was a slight increase in the systolic dimension of the left ventricular cavity and both end systolic and diastolic volumes (Figs 2 and 3) Even though these differences could be consid ered significant ($p < 0.05$) they are nevertheless small and may still be within the error of manual measurement

Three patients had asymmetric septal hyper trophy (septal to posterior wall thickness ratio more than 1 3) Two of these had systolic anterior motion of the mitral valve (Fig 4)

However in these patients the septal motion was normal unlike that seen in idiopathic hyper trophic subaortic stenosis

In Group A the indices of contractility (short ening fraction ejection fraction circumferential fiber shortening and velocities of the septum and posterior wall) were all normal In contrast the patients with cardiomyopathy had markedly dilated left ventricles thickened septa and poste rior walls and greatly depressed indices of contractility (Fig 5)

When non cardiac alcoholic subjects were divided according to the duration of drinking (Table IV) there were no significant differences either in echocardiographic parameters or in systolic time intervals between the group drink ing for 5 to 14 years and that drinking for 15 to 30 years

Discussion

Cardiac dysfunction in asymptomatic alcoholic subjects had been known since Spodick and asso ciates and later others[3,4] reported prolonged pre ejection period shortened ejection time and increased PEP/LVET ratio Our results are very similar

The objective of this study was to find out whether corresponding abnormalities of cardiac function could be established by echocardiogra phy Marked increase of the thickness of the interventricular septum and the left ventricular wall were observed together with a small increase in the size of the left ventricular cavity and a corresponding marked increase of the left ventric ular mass

VCF (Circ/Sec)	LVDVI (ml/M²)	LVSVI (ml/M²)	SVI (ml/M²)	EF	LV mass I (gm/M²)	VpW (cm/sec)	VIS (cm/sec)
1.39	65	22.5	43.3	0.66	145.7	0.89	0.64
0.29	16	8.2	10.6	0.08	32	0.22	0.25
1.19	57.8	18.9	40	0.6[illegible]	101	0.83	0.56
0.15	13.2	5.5	12.6	0.07	20.7	0.15	0.16
0.59	124.1	93.1	31	0.25	242	0.39	0.21
0.21	18.6	15.6	10	0.07	53	0.16	0.09
NS	<0.05	<0.05	NS	NS	<0.001	NS	NS
<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Chronic alcoholic subjects without cardiac symptoms were examined echocardiographically in two studies[13, 14] Those studies were published only in abstract form and the number of subjects was small Mathews and co workers[13] studied 26 chronic non cardiac alcoholic subjects and found increased thickness of the septum and the left ventricle in 81% Our results are similar but the incidence of this abnormality was approximately 45% in our study This increased thickness is probably due to hypertrophy of the myocardium as is evident from pathological reports of Schenk and Cohen[7] However glycoprotein deposition demonstrated in a chronic animal experiment by Regan and colleagues[15] may be considered as potentially responsible for the increased thickness

In the absence of any other apparent causes it seems likely that cardiac hypertrophy in subjects studied was due to the influence of alcohol

Knowing that systolic time intervals are abnormal in chronic alcoholic subjects we expected to find an evidence of decreased myocardial contractility on echocardiogram However all echocardiographic indices of contractility appear to be normal and do not differ from a control group Fernando and Friedman[4] reported even hyperdynamic echocardiograms in alcoholic patients with cirrhosis of the liver

Having the benefit of recording both systolic time intervals and the echocardiogram we would like to explain why the indices of cardiac contractility are echocardiographically normal while systolic time intervals are abnormal It appears that either systolic intervals are more sensitive in evaluating myocardial contractility or that abnormal systolic time intervals are due to other causes than decreased contractility The former alternative even though quite possible has not been investigated and latter seems to be likely

Regan and associates[5, 15] postulated that abnormal systolic time intervals in alcoholic subjects are due to abnormal compliance of the left ventricle

The main finding of our study is the presence of myocardial hypertrophy in chronic alcoholic individuals myocardial hypertrophy being one of the most important causes of decreased compliance[16]

Furthermore abnormal systolic time intervals may be due not only to decreased contractility but also due to decreased compliance of the myocardium[17] Finding marked hypertrophy of the heart normal indices of contractility by echocardiogram and abnormal systolic time intervals lead us to concur with the Regan hypothesis of decreased myocardial compliance as the possible mechanism of abnormal myocardial function in chronic alcoholic persons

Our three cases of asymmetrical septal hypertrophy (two with anterior systolic motion of the mitral valve) are of interest and add to the ever growing list of conditions simulating hypertrophic cardiomyopathy There is however a difference between our cases and patients with hypertrophic cardiomyopathy The septal motion is normal or increased in our subjects but diminished in cases of hypertrophic cardiomyopathy

Surprisingly there was no increase in cardiac abnormalities paralleling longer periods of alcoholism When the two groups were compared the first drinking for 5 to 14 years and the second drinking for 15 to 30 years there were virtually no differences in systolic time intervals or in echocardiographic findings It may appear that whatever hypertrophy occurs in chronic alcoholic subjects

Table IV Comparison of noninvasive studies according to duration of drinking*

	No	Age	Years of drink	PEP	LVETI	PEP/LVET	C/T	Dd	Ds	IVSt
Group I (5-14 years of drinking)	32	30 1 4 4	8 9 3.1	0 106 0 014	0.399 0 027	0.394 0 056	0 45 0 047	49 0 4 7	31.5 3 8	11 7 1.5
Group II (15-30 years of drinking)	41	3"6 5 0	20 3 4.8	0 10" 0 011	0 401 0 031	0.396 0 056	0 45 0 041	49 8 5.9	30 8 5 5	11" 1.2
p value		<0 001	<0 001	NS	NS	NS	NS	NS	NS	NS

Mean and standard deviation.

* Abbreviations in Tables I and II

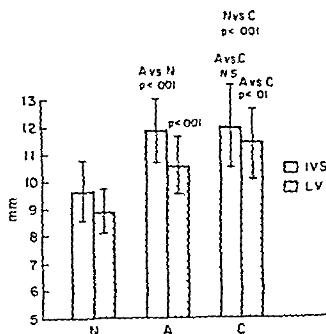


Fig 2 Thickness of the interventricular septum (IVS) = open bars and thickness of the posterior wall of the left ventricle (LV) = shaded bars, in three groups N = normal controls A = alcoholics C = alcoholics with congestive heart failure Vertical lines = standard deviation.

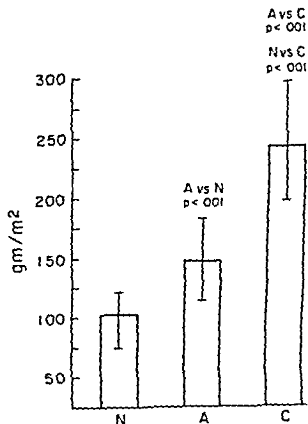


Fig 3 Left ventricular mass Index (gm./M) Abbreviatio as in Fig 2.

takes place in the first five years of the addiction This conclusion however should be considered with caution because the information about duration of drinking cannot be considered very accurate since it depends to a large extent on the memory and interpretation of the subjects

It is of interest that when former chronic alcoholic individuals abstained from drinking for a longer period the echocardiogram showed no abnormalities [9] This may suggest a reversibility of earlier stages of cardiac involvement in chronic alcoholic subjects

When comparing a group of non-cardiac alcoholic subjects with those with alcoholic cardi myopathy it is apparent that a major difference marked dilatation of the heart and decreas myocardial contractility in cardiomyopathy H pertrophy is present in both, however but mo severe in the cardiomyopathy group

Summary

The echocardiogram and systolic time interva were used to evaluate cardiac function in

LVt	*VCF*	*SF*	*LVDVI*	*LVSVI*	*SVI*	*EF*	*LV mass I*	*VLW*	*VIVS*	*SV + RV*
10 6	1 32	35 7	64 6	22 9	41 7	0 64	145 5	0 87	0 63	34 4
1 2	0 19	3 9	14 1	6 6	9 5	0 05	27 6	0 16	0 19	9 4
10 3	1 44	38 1	65 4	21 1	44 5	0 67	145 8	0 90	0 66	31 4
0 9 NS	0 34 NS	7 7 NS	17 2 NS	9 2 NS	11 2 NS	0 09 NS	35 0 NS	0 25 NS	0 29 NS	8.4 NS

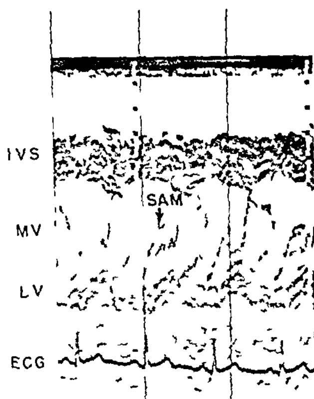


Fig 4 Echocardiogram of a chronic alcoholic subject Systolic anterior motion of the mitral valve (*SAM*) marked with *an arrow* Note septal hypertrophy Abbreviations as in *Fig 1*

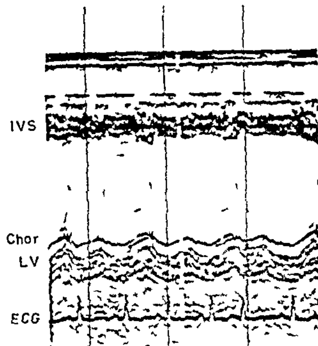


Fig 5 Alcoholic cardiomyopathy Markedly dilated poorly contracting left ventricle Abbreviations as in *Fig 1*

chronic alcoholic subjects without symptoms of heart disease All were below the age of 45 years and none had arterial hypertension or history of heart disease The echocardiograms of chronic alcoholic individuals revealed increased thickness of the left ventricular wall (10 4 mm ± 1 05 normal controls 8 76 mm ± 86 $p < 0\ 001$) inter ventricular septum (11 71 mm ± 1 33 normal controls 9 63 ± 1 24 $p < 0\ 001$) and markedly increased left ventricular mass (145 gm /M² ± 32 normal controls 101 ± 20 7 $p < 0\ 001$)

The echocardiographic indices of myocardial contractility (ejection fraction, wall excursion and velocity circumferential fiber shortening) were normal Systolic time intervals revealed shortening of ejection time and prolongation of the pre ejection period It was found that approximately half of the asymptomatic alcoholic subjects have left ventricular hypertrophy without echocardiographic evidence of decreased myocardial contractility It is suggest that

abnormal systolic time intervals may be due to decreased myocardial compliance

The authors would like to thank Dr Jacob Grossman for his critical review of the manuscript and Ms Faye Fried Ms Nelsa Padin and Ms Arlene Kallman for their assistance

REFERENCES

1 Burch G E and Walsh J J Cardiac insufficiency in chronic alcoholism Am J Cardiol 6 864 1960
2 Goodwin J F Alcohol and the heart Alcoholic cardiomyopathy J R Coll Phys 12 5 1977
3 Regan T J, Levinson G E Olderwurtel H A Frank M J Weisse A B and Moschos, C B Ventricular function in noncardiacs with alcoholic fatty liver Role of ethanol in production of cardiomyopathy J Clin Invest 48 397 1969
4 Spodick D H Pigott V M and Chirife R Preclinical cardiac malfunction in chronic alcoholism N Engl J Med 287 677 1972
5 Wu C F Sudhaker M Jafen G Ahmed S S, and Regan T J Preclinical cardiomyopathy in chronic alcoholics a sex difference AM HEART J 91 281 1976
6 Levi G F, Quadri A Ratti, S and Basagni M Preclinical abnormality of left ventricular function in chronic alcholics, Br Heart J 39 35 1977
7 Schenk E A, and Cohen J The heart in chronic alcoholism Clinical and pathological findings Path Microbiol 35 96, 1970
8 Weissler A M Harris W G and Schoenfeld C D Bedside technics for evaluation of ventricular function in man Am J Cardiol 23 577 1969
9 Sahn D J DeMaria A, Kisslo J and Weyman A Recommendation regarding quantitation in M mode echocardiography Circulation 58 1072, 1978
10 Teicholz, L E Kreulen T, Herman M V and Gorlin R Problems in echocardiographic volume determinations echocardiographic angiographic correlations in the presence or absence of asynergy Am J Cardiol 37 7 1976
11 Feigenbaum H Echocardiography Lea & Febiger 1976 Page 320
12 Troy B L Pombo J and Rackely C E Measurement of Left Ventricular Wall Thickness and Mass by Echocardiography Circulation 45 602 1972
13 Mathews F C Jr Henry W L Delnigro A A, Fletcher R D Snow J A, and Epstein S E Echocardiographic abnormalities in asymptomatic chronic alcoholics (Abstr) Clin Res April, 1976, pp 229A
14 Fernando H A, and Friedman H S Demonstration of the hyperdynamic heart of cirrhosis by echocardiography (Abstr) Clin Res 24 613A 1976
15 Regan T J, Khan M I, Ettinger P O, Haider B Lyons, M M and Olderwurtel H A Myocardial function and lipid metabolism in the chronic alcoholic animal, J Clin Invest 54 740 1974
16 Grossman W, McLaurin L P Moos S P, Stefadouros, M and Young D T Wall thickness and diastolic properties of the left ventricle Circulation 49 129 1974
17 Lewis R P A critical review of systolic time intervals Circulation 56 146 1977
18 Bush, C A, and Lewis R P Importance of preload in chronic left ventricular disease Circulation 48(Suppl IV) IV 151 1973
19 Reeves, W C, Nanda N C, and Gramiak R Echocardiography in chronic alcoholics following prolonged periods of abstinence AM HEART J 95 578 1978

Truncus arteriosus malformation a spectrum including fourth and sixth aortic arch interruptions

Kate Rothko M D
G William Moore M D Ph D *
Grover M Hutchins M D
Baltimore Md

Truncus arteriosus malformation is a relatively rare form of congenital heart disease accounting for approximately 1% to 2% of autopsied patients with congenital heart defects[1] The exact anatomic pattern of the great vessels varies and Van Praagh and Van Praagh[2] were the first to emphasize the inverse variation in development of the fourth and sixth aortic arches in this malformation The impetus for persistence of both arches during fetal life is removed in truncus arteriosus malformation [3] so that most cases show a well developed fourth arch with absence or only a ligamentous remnant of the ductus arteriosus however two recent series report 14 to 23% of cases having a well developed sixth aortic arch associated with interruption of the ascending aorta Collett and Edwards noted only one such case

Concepts of the pathogenesis of truncus arteriosus include primary deficiency of the conotruncal ridges[3] or primary failure of formation of the pulmonary conus Other studies on normal cardiogenesis and on truncus arteriosus malformation [3] have postulated a hemodynamic basis for the configuration of both the great vessels and the semilunar valves In the present study all cases of truncus arteriosus malformation listed in the autopsy files of The Johns Hopkins Hospital were reviewed and interpreted in relation to the three theories of pathogenesis. The results suggest that a hemodynamic explanation may account for the preferential development of either the fourth or the sixth aortic arch in truncus arteriosus malformation

Materials and methods

All patients with truncus arteriosus malformation listed in the autopsy files of The Johns Hopkins Hospital for whom the heart was available for review were included in this study Cases with either pulmonic or aortic atresia were omitted Nineteen patients met the criteria for this study The patients ranged in age from one day to 30 years old and included 12 males Seven patients had no cardiac operations In seven patients pulmonary artery banding only was performed Three patients had right subclavian to pulmonary artery anastomoses and one had a descending aorta to left pulmonary artery anastomosis One patient had total correction with right ventricle to pulmonary artery homograft ligation of the proximal pulmonary trunk and patching of the ventricular septal defect Gross heart specimens were reviewed and a standard series of observations was made on each including preferential aortic arch development (fourth vs sixth) origin of truncus from either left ventricle predominantly right ventricle predominantly or straddling the ventricular septum state of interventricular septum number of semilunar valve cusps and origins of the coronary arteries Also

From the Department of Pathology of The Johns Hopkins Medical Institutions, Baltimore Maryland

Supported by Grant 1 RO1 HL 22963 from The National Institutes of Health, Public Health Service Department of Health, Education and Welfare

Received for publication June 8, 1979

Accepted for publication July 24 1979

Reprint requests Dr Grover M Hutchins, Department of Pathology The Johns Hopkins Hospital Baltimore Maryland 21205

Dr Moore is a Research Fellow of the American Heart Association, Maryland Affiliate In

0002-8703/80/010017 + 08$00.80/0 © 1980 The C V Mosby Co

Table I Patients with truncus arteriosus malformation

Case	Age race sex	Interatrial septum	Intervent septum	Truncus valve cusps	Cusp of origin of PT	Side of aortic arch	% valve overrides the RV	Diameter	
								Aorta mm	PT mm
Interrupted sixth aortic arch (absent ductus arteriosus)									
1	17Y WM	PFO	VSD	R L,A	L	L	50	32	2?
2	5W WF	PFO	VSD	R P L	L	R	75	09	05
3	12D WM	PFO	VSD	R L,A	A	R	60	11	08
4	3M WF	NL	VSD	R P L	L	L	50	08	07
5	16Y BM	PFO	VSD	R P L	R †	R	60	12	06
6	12D WM	PPFO	VSD	R P L,A	A	L	7?	10	04
7	8D WM	PFO	VSD	R P L,A	A	L	50	08	03
8	6W WM	PFO	VSD	R P L,A	L	L	50	14	09
9	2Y WM	PPFO	VSD	R L,A	L	L	75	23	0?
10	13D BF	PPFO	VSD	R L,A	A	L	85	08	05
11	5W WM	PFO	VSD	R P L,A	L	L	65	11	03
12	3M WM	PPFO	VSD	R P L A	A	L	50	14	08
13	2D WM	ASD	CANAL	R P L	L	L	100	08	06
Uncertain status of ductus arteriosus									
14	1M WF	ASD	VSD	R P,A	A	L	90	?	?
15	12Y BM	NL	VSD	R P L	L	L	25	22	19
16	18Y WM	NL	VSD	R P L	L	L	75	?	?
Ductus arteriosus present									
17	4M WF	PPFO	VSD	R P,L-A	A	L	90	13	08
Interrupted fourth aortic arch									
18	1D WF	PFO	VSD	R P L,A	–	–	100	04	12
19	30Y WF	PPFO	VSD	R P L,A	–	–	100	22	24

Abbreviations A = anterior ASD = secundum atrial septal defect B = black D = day F = female L = left M = male or months NL = normal P = posterior PFO = patent foramen ovale PPFO = probe patent foramen ovale PT = pulmonary trunk R = right RV = right ventricle SB = stillborn VSD = ventricular septal defect W = white or weeks Y = year

Cusps listed in order clockwise from R Right and left coronary arteries arise from the corresponding sinuses Hyphen indicates the position of a raphe

†See description in Results section

recorded were the status of the interatrial septum, the foramen ovale and the ductus arteriosus A computer program written in FORTRAN IV computer language and implemented on the IBM 360/148 computer at the Information Systems Department of The Johns Hopkins Medical Institutions was used to tabulate the specific anatomy of each case of truncus arteriosus malformation and the associations with other significant congenital cardiac lesions The implied relationships among 288 observational and combinatorial statements tabulated for each heart were expressed in symbolic logic[15] We employed additional statements and relationships expressed in symbolic logic to construct the sequence of normal human cardiac development as determined from embryologic studies[11] and to compare hypothetical embryonic pathways postulated by the three theories of pathogenesis of truncus arteriosus malformation For each pathogenetic theory our analysis determines the number of *primary events* or spontaneous deviations from normal development, *required to* explain the lesions observed in each patient We used the proposition that the most efficient and probably the best explanation for a malformation complex is that theory which explains most lesions as secondary events and thus accumulates the fewest primary events Comparison of theories was made statistically with the chi square goodness of fit test

Results

The 19 patients in this study were divided into *four groups on the basis of the anatomy of the* aortic arch (Table I) Two patients showed sixth

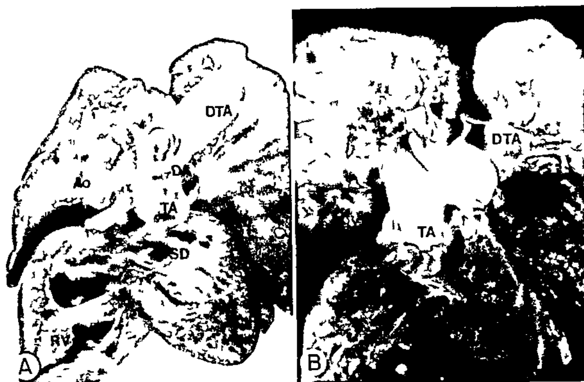


Fig 1 A and B *A* Case No 18 with an interrupted fourth aortic arch. The descending thoracic aorta *(DTA)* arises from the widely patent ductus arteriosus *(DA)* The pulmonary arteries arise from the truncus arteriosus *(TA)* as does the ascending aorta *(Ao)* which gives origin to the great arteries The distal aortic arch is absent *B* Case No 11 with an interrupted sixth aortic arch. The pulmonary arteries arise just above the truncal valve The ductus arteriosus is absent *IVS* = interventricular septum RV = right ventricle VSD = ventricular septal defect

arch dominance with an interrupted aortic arch while the remainder showed dominance of the fourth aortic arch (Fig 1) The relative diameter of the aortic and pulmonary trunks were in keeping with the arch dominance—in other words only cases with sixth arch dominance showed a pulmonary trunk with a larger diameter than the aortic trunk and in all other cases the aorta was the larger vessel There were no other anatomic features which invariably distinguished sixth arch dominant from fourth arch dominant cases

The ductus arteriosus showed complete agenesis in 13 cases and was patent in three cases including the two cases with sixth arch dominance The status of the ductus could not be determined in the three remaining cases The aortic arch was left sided in 14 cases and right sided in three cases The remaining two cases were those with interrupted aortic arch

All cases showed a ventricular septal defect The site of origin of the truncus arteriosus over this defect varied from predominantly right ventricular in 11 cases to predominantly left ventricular in one case In six cases the truncus arose equally from the two ventricles Among the 11 cases arising primarily from the right ventricle three arose exclusively from that ventricle

The truncus valves were either tricuspid or quadricuspid in all cases There were eight cases with quadricuspid semilunar valves five of which had raphes between various cusps Two of the 11 tricuspid truncal valve cases had a single raphe Mitral truncal valve continuity was fibrous in all 18 cases in which the question was applicable The nineteenth case had a single atrioventricular valve which was in fibrous continuity with the truncal valve There were 10 cases with a muscular band and one with a fibrous band intervening between the tricuspid and truncal valves The remaining seven cases showed tricuspid truncal fibrous continuity

In all cases except Case No 14 right and left coronary arteries with normal distribution arose from the sinuses of the right and left cusps respectively In Case No 14 a single coronary artery arose from the right sinus and gave o

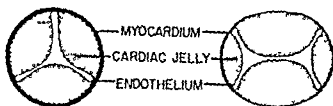


Fig 2 Diagram showing the arrangement of endocardium and cardiac jelly to be expected if the outflow tract is round or elliptical

right and left coronary arteries several millimeters distal to the ostium The origin of the pulmonary trunk relative to the truncal valve cusps was also variable In most cases the pulmonary trunk arose over either the left or the anterior valve cusp

There were eight cases with a patent foramen ovale and six cases in which the foramen was probe patent but guarded by membrane In three cases the septum was closed The remaining two cases had larger atrial septal defects—one secundum type and one canal type

The autopsy files were reviewed for documentation of associated extracardiovascular congenital anomalies In two patients (Cases No 15 and 19) only heart and lungs were examined so the question could not be addressed Of the remaining 17 patients five showed anomalies in other organs Two showed cystic ovaries (Cases No 4 and 14) and in Case No 4 there was associated cytomegaly of the adrenals Another patient (Case No 2) showed a hypoplastic left ear and focal renal dysplasia Case No 8 had a partial DiGeorge syndrome with absent parathyroid glands thymic hypoplasia and poorly developed T cell regions of lymphoid tissue as well as angioid changes in the lymph nodes and a patent urachus Finally Case No 13 whose cardiac anomalies are described in greater detail below showed unilateral renal agenesis ureteral duplication and islet cell hyperplasia and hypertrophy

Two patients were of special interest Case No 13 was a 2 day old white male product of a 36 to 37 week gestation who presented with respiratory distress syndrome at birth Examination of the umbilical cord revealed a single artery and vein In addition to the truncus arteriosus malformation and the extracardiac anomalies described above the heart showed a primitive atrioventricular canal defect including a septum primum defect and a large canal type ventricular septal defect (19)

Case No 5 was a 16 year old black male with severe growth retardation and exercise intolerance who died of cerebral abscesses All congenital anomalies found at autopsy were in the cardiovascular system The truncus arteriosus arose equally from the two ventricles and gave rise directly to a small stenotic right pulmonary artery There was a small outpouching of the truncus in the region of the expected left pulmonary artery but this vessel was absent with the left lung supplied by the bronchial circulation only There was also a right sided aortic arch

Discussion

Embryo reconstruction studies by DeVries and Saunders[1] and Goerttler s glass models[11] support the hemodynamic theory of normal cardiogenesis and the development of the spiral course of the great vessels leaving the two ventricles The relative orientations of the two ventricles in the normal heart (left posterolateral to right) and the sequential bendings of the heart loop are the key factors in creating two spiral outflow streams which enter the two great vessels Right ventricular outflow enters the sixth arch preferentially while left ventricular outflow is directed into the fourth arch[1 2] Septa arise from the deformable cushion material in areas of low flow between these two streams and partition the ventricles semilunar valves and great vessels[1 2]

Study of a 23 mm human embryo with truncus arteriosus malformation[11] provides direct support for the concept that a defect in placement of the cardiac chambers which redirects the normal ventricular outflow patterns may lead to abnormal cardiogenesis with failure of septation of the ventricular outflow tracts the semilunar valves and the great vessels leaving the base of the heart Due to abnormal relative ventricular positions the two ventricular outflow streams fuse at the semilunar valve level rather than spiraling about one another In the presence of this fused stream there is no region of low blood flow into which the outflow tract cushions can protrude fuse and form the muscular septum which in the normal heart lies between the aortic and pulmonic valves The end result is a single great vessel leaving the base of the heart with a single semilunar valve and in essence a single ventricular outflow tract (two tracts connected by a ventricular septal

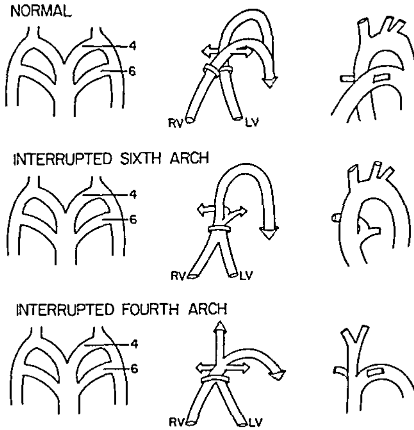


Fig 3 Diagram of bilaterally symmetrical aortic arches *(left)* pathways of blood flow from the ventricles into the arches *(center)* and the arrangement of blood vessels found after obliteration of the unused channels *(right)* In the normal *(top)* the ventricular ejection streams are separate In the two forms of truncus arteriosus malformation the ventricular ejection streams fuse and prevent septation of the interventricular communication semilunar valves, and proximal aortic sac In sixth arch interruption *(middle)* the predominant direction of the fused outflow stream is into the fourth arches in fourth arch interruption *(bottom)* the fused stream of blood flow is predominantly into the left sixth arch.

defect) An alteration of ventricular positions from normal has also been illustrated in a canine embryo with truncus arteriosus malformation

The number of truncal valve leaflets found in this series was consistently three or four These two most common valve cusp configurations may be understood in hemodynamic terms if one postulates a slight difference in the timing of events in the two situations In the tricuspid case fusion of ventricular outflow streams is postulated to occur before development of the four conotruncal swellings has begun at a time when the outflow tract is still round Here the path of least resistance for the fluid stream is through the center of the tube and the configuration of least energy [1] for the cushion material is a tricuspid one (Fig 2) In the quadricuspid case on the other hand fusion of the streams may occur somewhat later at a time when the outflow tract has already assumed its elliptical shape In a tube of this shape the flow pattern of least resistance is not a cylinder through the center but itself tends to be more elliptical Simultaneously the cushion material assumes the configuration of lowest energy which in this case is a quadricuspid configuration Due to the fused ventricular outflow stream however the opposing conotruncal swellings are unable to fuse because there is constantly some central flow between them

Since the presence of a single trunk leaving the base of the heart allows extensive communication between systemic and pulmonary circulations it is apparently unnecessary for the ductus arteriosus to persist during fetal life in cases of truncus arteriosus In fact most cases of truncus art sus show agenesis of the ductus arteriosu

the fourth aortic arch is well developed There are only a few cases amounting to less than 10% [4,5] in which the ductus is patent despite a well developed aortic arch In our series of 19 cases only the two cases with sixth aortic arch dominance and a single case with fourth arch dominance had an associated patent ductus arteriosus A smaller number of cases 14 to 25% in other series[2,4,7] and approximately 10% in our study show interrupted aortic arch with persistence of the left sixth arch or ductus arteriosus The more frequent finding of fourth aortic arch development and sixth arch absence implies that the single fused ventricular outflow stream is most often angled toward the fourth arch rather than the sixth (Fig 3) In a limited number of cases however, the reverse must be true The cardiac anomaly of interrupted aortic arch itself is frequently associated with other intracardiac anomalies which shunt blood from the left to right side of the heart [4,5] Since the right ventricular outflow normally enters the sixth aortic arch preferentially in these cases the sixth arch is kept widely patent while the fourth receives subnormal flow If these flow patterns are set up before Carnegie Stage 17 (approximate ovulation age 35 days and crown rump length 12 mm)[11] it is possible that the fourth aortic arch may disappear completely [4]

The situation in truncus arteriosus malformation is somewhat more complex than in interrupted aortic arch since we are dealing with a single outflow stream Thiene and co workers[2] have commented on the right ventricular origin of the truncus in several cases with sixth arch dominance both in their report and in the literature However as our study suggests this is not a universal finding and multiple cases of fourth arch dominant type both in the literature and in our study have right ventricular origin In the embryo with truncus arteriosus malformation [1] the fused stream was directed toward the fourth aortic arch as must be the case in the majority of truncus arteriosus cases It is not hard to imagine however that a slightly different ventricular orientation might also lead to a fused outflow stream tilted at an angle to favor flow to the sixth aortic arch over the fourth

There are three major theories which explain the pathogenesis of truncus arteriosus malformation fusion of outflow streams as discussed above absence or hypoplasia of conotruncal ridges and absence of the pulmonary conus The anatomic abnormality in the truncus arteriosus malformation consists of a defect in separation of the outflow tract the valve and the great vessels The fusion of outflow streams theory accounts for failure of septation of these three areas in terms of a single primary event namely the undivided stream of blood On the other hand, theories which involve the absence of conotruncal ridges or the pulmonary conus require at least two primary structural defects to account for the nonseptation of the three anatomic regions In evaluating the relative superiority of the three pathogenetic theories however, it is also important to consider the associated malformations We employed a computer program with a symbolic logic translation of the three pathogenetic theories of truncus arteriosus malformation to tabulate the associated anatomic cardiovascular lesions unexplained by each of the theories None of the theories explains the occasional extracardiovascular anomalies atrial septal defect patent foramen ovale or atrioventricular canal defect

The theory of absence or hypoplasia of the conotruncal ridge appears to explain all other associated cardiovascular anomalies with the exception of the two aortic arch anomalies interruption of the aortic arch and right aortic arch A bicuspid tricuspid or quadricuspid valve may be explained as follows A bicuspid valve occurs when the truncal swellings or the intercalated valve swellings do not develop at all a tricuspid valve results when one of the four valve swellings fail to develop completely a quadricuspid results when all four swellings develop but are hypoplastic and fail to fuse Absence of the ductus arteriosus is explained hemodynamically in terms of disuse obliteration In the face of a direct left to right communication in truncus arteriosus during fetal life the persistence of the ductus arteriosus is superfluous Proponents of the absence of conotruncal ridges theory consider the great vessel malformations as separate anomalies requiring separate developmental events and they do not attempt to explain either interrupted aortic arch or right sided aortic arch in terms of the primary hypothesis

The theory of absence of pulmonary conus suggested by Van Praagh and Van Praagh explains the bicuspid and tricuspid truncal valves

but the quadricuspid valve requires the additional primary event of incorporating a remnant of pulmonary leaflet. This theory incorporates great vessel anomalies as part of the malformation and in fact emphasizes the significance of the interrupted aortic arch variant, although its pathogenesis is not explained in detail. The absence of conotruncal ridges and absence of pulmonary conus theories are fundamentally defective blueprint theories while the fusion of outflow streams theory is a hemodynamic theory.[16]

The theory of fusion of outflow streams suggested previously[13,14] has been discussed in greater detail above. This theory's explanation of formation of both tricuspid and quadricuspid valves is presented above and depends upon the precise timing of fusion of the ventricular outflow streams. The fusion of outflow streams theory explains associated abnormal findings in the great vessels in terms of the angle at which the fused ventricular outflow stream leaves the base of the heart. The initiating event may be either a delay in growth and closure of the endocardial cushions in relation to caudal descent of the heart[14] or abnormal relative ventricular orientations.[3] In either case the hemodynamic events following upon each explain both the truncus arteriosus malformation itself and the associated anomalies in the great vessels.

In summary, explanation of the pathogenesis of truncus arteriosus malformation by either the absence of conotruncal ridges or the absence of pulmonary conus theories would require two separate primary events. In contrast, the fusion of outflow theory requires only a single primary event. All three theories fail to account for interatrial septal defects and for a canal type ventricular septal defect. All theories successfully account for the tricuspid truncus valve and agenesis of the ductus arteriosus. Without additional primary events, the absence of conotruncal ridges theory fails to account for interrupted aortic arch, while the absence of pulmonary conus theory fails to account for the quadricuspid truncus valve. Tabulation of these primary events for the 19 cases of truncus arteriosus malformation in the present series gives 31 for the fusion of outflow streams theory, 54 for the absence of conotruncal ridges theory, and 60 for the absence of pulmonary conus theory. The fusion of outflow streams theory is therefore statistically superior to both the absence of conotruncal ridges and absence of pulmonary conus theories (χ^2_{1df} = 6.22, 9.24; $p < 0.05$, $p < 0.005$, respectively). If the eight occurrences of patent foramen ovale are neglected, the results are even more significant. The smaller number of primary events required by the fusion of outflow streams theory of the pathogenesis of truncus arteriosus makes it the most attractive explanation and lends additional support to the importance of mechanical forces in normal and abnormal cardiogenesis.

Summary

Previous explanations of the pathogenesis of truncus arteriosus malformation have emphasized absence of conotruncal ridges, absence of pulmonary conus, or fusion of ventricular outflow streams. These concepts explain the persistence of the single semilunar valve and outflow vessel but have not elucidated the significance of many associated anatomic lesions. We studied the 19 patients with truncus arteriosus malformation listed in the autopsy files of The Johns Hopkins Hospital whose hearts were available for review. The patients ranged in age from one day to 30 years and included 12 males. All hearts showed a single semilunar valve with three or four cusps and a high ventricular septal defect. In 13 patients the aorta was larger in diameter than the pulmonary artery and no remnant of the ductus arteriosus was present (interruption of the embryonic sixth arch). In one patient the aorta was larger than the pulmonary artery, and a small patent ductus arteriosus was present. In two patients the pulmonary artery was larger than the aorta and the aortic arch was interrupted. The remaining three cases could not be fully evaluated for the status of the ductus arteriosus and size of the great arteries. We tabulated the number of associated anatomic lesions which were unexplained by each of the three pathogenetic hypotheses. The fused outflow stream hypothesis, which explains truncus arteriosus malformation as the result of a maldirection of ventricular outflow streams so that the separation of two semilunar valves is prevented, was superior at the 0.05 level of significance. This concept explains the spectrum of great vessel patterns in which flow is dominant into either the sixth or fourth embryonic aortic arch, permitting early disappearance of unperfused segments of

the aortic arches and is commonly seen at autopsy as either an interrupted aorta or an absent ductus arteriosus

REFERENCES

1 Tandon R Hauck A J and Nadas A S Persistent truncus arteriosus. A clinical hemodynamic and autopsy study of nineteen cases Circulation 28 1050 1963
2 Van Praagh R and Van Praagh S The anatomy of common aorticopulmonary trunk (truncus arteriosus communis) and its embryologic implications A study of 57 necropsy cases Am J Cardiol 16 406 1965
3 Van Mierop L H S Pathology and pathogenesis of the common cardiac malformations Cardiovasc Clinics 2 27 1970
4 Bharati S McAllister H A Rosenquist G C Miller R A Tatooles C J, and Lev M The surgical anatomy of truncus arteriosus communis J Thorac Cardiovasc Surg 67 501 1974
5 Collett R W and Edwards J E Persistent truncus arteriosus A classification according to anatomic types Surg Clin North Am 29 29 1245 1949
6 Crupi G Macartney F J and Anderson R H Persistent truncus arteriosus A study of 66 autopsy cases with special reference to definition and morphogenesis Am J Cardiol 40 569 1977
7 Keith J D Rowe R D and Vlad P Heart Disease in *Infancy and Childhood 3rd edition New York* 1978 Macmillan Co pp 456 464
8 Lev M and Saphir O Truncus arteriosus communis persistens J Pediatr *20* 74 1942
9 Nadas A S Pediatric Cardiology 2nd edition Philadelphia 1963 W B Saunders Company p 50
10 DeVries P A, and Saunders J B C M Development of the ventricles and spiral outflow tract in the human heart A contribution to the development of the human heart from age group IX to age group XV Contrib Embryol Carnegie Inst Wash 37 87 1962
11 Goerttler K Glass model experiments of embryonic human hearts *in* Cardiac Development with Special Reference to Congenital Heart Disease O C Jaffee ed Dayton 1972 University of Dayton Press p 29-43
12 Maron B J and Hutchins G M The development of the semilunar valves in the human heart Am J Pathol 74 331 1974
13 Maron B J and Hutchins G M Truncus arteriosus malformation in a human embryo Am J Anat 134 167 1972
14 Steiner P and Finegold M J Truncus arteriosus with atresia of the aortic arch Arch Pathol 79 518 1965
15 Moore G W Hutchins G M and Bulkley B H Application of symbolic logic to the pathogenesis of congenital heart disease tetralogy *of Fallot Metamed* 1 313 1977
16 Moore G W Hutchins G M and Bulkley B H Certainty levels in the nullity method of symbolic logic Application to the pathogenesis of congenital heart malformations J Theor Biol 76 53 1979
17 Streeter G L Developmental Horizons in Human Embryos Age Groups XI to XXIII Carnegie Institution of Washington Embryology Reprint Vol II Baltimore 1951 The Lord Baltimore Press
18 Meredith M A Hutchins G M and Moore G W Role of the left interventricular sulcus in formation of the interventricular septum and crista supraventricularis in normal human cardiogenesis Anat Rec 194 417 1979
19 Hutchins G M Liebman L Moore G W and Gharagozloo F Atrioventricular canal malformations explained by reduced compression upon the developing heart Am J Pathol 95 579 1979
20 Van Mierop L H S Patterson D F and Schnarr W R Pathogenesis of persistent truncus arteriosus in light of observations made in a dog embryo with the anomaly Am J Cardiol 41 755 1978
21 Thompson D A W On Growth and Form 2nd edition New York 1942 McMillan Co pp 465-644
22 Thiene G Bortolotti U Gallucci V Terribile V and Pellegrino P A Anatomical study of truncus arteriosus communis with embryological and surgical considerations Br Heart J 38 1109 1976
23 Moore G W and Hutchins G M Association of interrupted aortic arch with malformations producing reduced blood flow to the fourth aortic arches Am J Cardiol 42 467 1978
24 Moller J H and Edwards J E Interruption of aortic arch Anatomic patterns and associated cardiac malformations Am J Roentgenol 95 557 1965
25 Celoria G C and Patton R B Congenital absence of the aortic arch, Am Heart J 58 407 1959
26 Rodbard S Vascular caliber Cardiology 60 4 1975
27 Congdon E D Transformation of the aortic arch system during the development of the human embryo Contributions to Embryology Vol 14 Carnegie Inst Wash Pub No 277 pp 47 110

Congenital aneurysms of the left ventricle

Amarjit Singh M D
Harold Katkov M D
James H Zavoral M D
Shashikant M Sane M D
James D McLeod M D
Minneapolis Minn

Most left ventricular aneurysms are seen in the adult population and are due to coronary occlusion and myocardial ischemia Aneurysms of the left ventricle in childhood are rare and when present could be either congenital or due to weakness of the left ventricle wall as a result of ischemia or surgical incision Only a handful of cases of true congenital left ventricular aneurysms are reported in the literature We present here four cases and a review of the literature to outline the modes of presentation natural history complications and prognosis of this unusual condition

Case reports

Case history 1 T J This child was born on August 23 1977 with a birth weight of 7 pounds His growth and development was normal and he was first seen by one of us (J D M) with respiratory difficulty suggestive of croup At the age of 10 months the boy looked active alert and healthy His weight was 10 2 kilograms and his height was 76 cm The heart rate was 100 per minute and regular and the respiratory rate was 22 per minute There were no abnormal findings on examination except for the displacement of a diffuse apical impulse to the left of the mid clavicular line in the fifth intercostal space A Grade I/VI short systolic ejection type murmur was heard in the second left intercostal space

From the Department of Cardiology and Radiology Children s Health Center Minneapolis, and the Department of Pediatrics, Hennepin County Medical Center Minneapolis Minn

Received for publication June ?? 1979
Accepted for publication July ?0 1979

Reprint requests Amarjit Singh, M D Division of Cardiology Children s Health Center 2_5 Chicago Ave South Minneapolis Minn 55404

A chest x ray (Fig 1 *A* and *B*) revealed a mass at the apex of the heart that could not be distinguished from the cardiac silhouette Fluoroscopy showed this mass to contract with the heart An electrocardiogram (Fig 2) demonstrated inversion of T waves in all the chest leads A two dimensional echocardiogram (Fig 3 *A* and *B*) was obtained which demonstrated a separate cavity lying near the left ventricular apex and communicating with the main left ventricular cavity The walls of this cavity seemed to contract actively At heart catheterization the hemodynamic data were normal Left ventriculography (Fig 4 and Fig 5 *A* and *B*) in multiple views demonstrated a large out pouching of the ventricular apical region It contracted actively along with the contraction of the main left ventricular body The proximal coronary arteries were normal The patient has been followed conservatively and has remained asymptomatic

Case history 2 B A This child was first seen at the age of five years for evaluation of a heart murmur Past history revealed that the child was born on February 15 1963 after a pregnancy that was complicated by threatened abortion at three months of gestation Her birth weight was 7 pounds and 13 ounces The growth and development was normal At the age of four years she had an episode of generalized cyanosis and stiffening while at play in the nursery She awoke promptly without any residual effects The cause of this episode was not established and no treatment was given Our assessment showed a normal looking alert child with a heart rate of 90 per minute and regular The blood pressure was 80/50 mm Hg in the right arm The abnormal findings were confined to the cardiovascular system and

000?-8703/80/010025 + 08$00 80 0



Fig 1 Case 1 The chest x ray in posteroanterior *(A)* and left lateral view *(B)* showing a mass at the apex of the heart that cannot be distinguished on the cardiac silhouette The bulge at the apex is less dense than the rest of the heart shadow On the lateral view the posterior border of the mass is clearly demarcated.

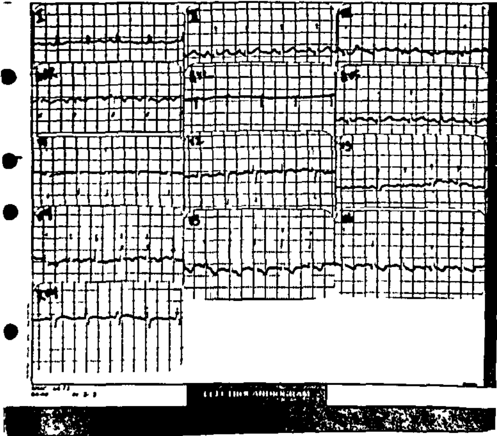


Fig 2 Case 1 The electrocardiogram showing increased voltages and inversion of T waves in the left chest leads

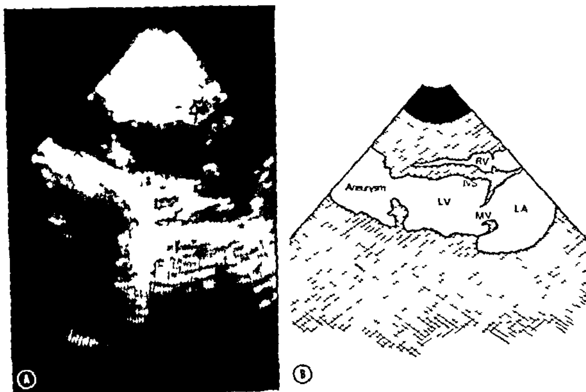


Fig 3 Case 1 Parasternal long axis two-dimensional echocardiogram *(A)* with accompanying schematic diagram *(B)* from Case 1 The aneurysmal cavity and the neck of the aneurysm are clearly seen separate from the cavity of the left ventricle proper The echocardiogram was obtained with a Varian 3000 machine and a 2.25 MHz frequency transducer *IVS* = Intraventricular septum *LA* = left atrium *LV* = left ventricle *MV* = mitral valve *RV* = right ventricle

included a diffuse apical impulse outside the nipple line in the sixth intercostal space A Grade II/VI high pitched systolic murmur was heard at the apex The heart sounds were normal

Chest x ray (Fig 6) revealed cardiomegaly with normal pulmonary vascularity The electocardiogram was normal except for some intraventricular conduction delay and flattening of the T waves in the left chest leads The hemodynamic data were normal on heart catheterization done shortly afterwards Ventriculography (Fig 7) demonstrated that extending from the left and anterior portions of the true left ventricular cavity was a very large highly trabeculated aneurysm that contracted with the left ventricular body Proximal coronary arteries were normal

This child did well over the next five years but electrocardiograms showed progressive inversion of T waves in the left chest leads and a heart catheterization to restudy the left ventricular function showed no significant change in its



Fig 4 Case 1 Left ventriculogram in systole showing the aneurysmal cavity separate from the left ventricular cavity proper Part of the aneurysm is contracting in systole but the most lateral part of its wall shows no evidence of motion There is thinning of the ventricular wall over the aneurysm



Fig 5 Case 1 The left ventriculogram in diastole in anteroposterior *(A)* and left lateral view *(B)* showing a fairly large left ventricular cavity and its relationship to the aneurysm The aneurysm is extending anteriorly as well as laterally The wall of the aneurysm is thinner compared to the wall thickness of the left ventricle The aneurysmal cavity is trabeculated The major coronary artery branches are normal

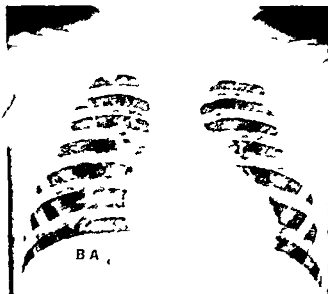


Fig 6 Case 2 The chest x ray in the anteroposterior view shows downward displacement of the cardiac apex and resembles dilatation of the left ventricle There is no evidence of ventricular aneurysm on the plain film

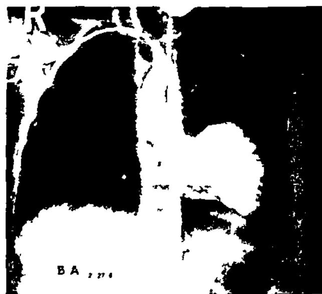


Fig 7 Case 2 Left ventriculogram demonstrating a large well trabeculated aneurysm of the left ventricle with significantly decreased size of the left ventricle cavity The entire left lateral wall and apex is formed by the aneurysm The major coronary artery branches are normal

contractility She was managed without surgery and when last seen at the age of 14 years she was asymptomatic normally active and was 51 kilograms in weight and 158 cm in height

Case history 3 J S The male child was born January 6 1964 after an uncomplicated pregnancy and delivery He had frequent upper respiratory infections in the first year of life and the chest x ray revealed an abnormal configuration (Fig 8*A*) Initial physical examination was normal



Fig. 8. Case 3. Chest x ray (A) demonstrating normal heart size with a density at the left border of the heart just above the apex. The ventriculogram (B) demonstrates an out pouching in the region of the density. This is different from the other cases in that it does not involve the apex of the ventricle but is situated higher on the anterior lateral wall. Note marked trabeculation of the aneurysm while the left ventricular cavity is normal and smooth walled.

except for displacement of the apical impulse to the left of the mid clavicular line. The heart sounds were normal and no murmur was heard. The electrocardiogram demonstrated deep Q waves in Leads I, aV_L, V and V and intraventricular conduction delay. A heart catheterization revealed normal hemodynamic data and ventriculography (Fig. 8B) demonstrated out pouching of the left ventricle with active contractions. This out pouching did not involve the left ventricle apex but was mainly situated higher on the anterolateral wall. The coronary arteries were normally distributed. The child was followed at yearly intervals and demonstrated normal growth and development. Subsequently he developed fatigue, dyspnea, and pallor after walking around without any significant change in the x ray or electrocardiographic findings. At the age of two years and two months he underwent open heart surgery and the surgeon described a large broad based out pouching of the left ventricle presenting in the angle between the anterior descending and the circumflex coronary arteries. It measured about 3 cm in diameter at its base. There seemed to be paradoxical motion in one portion of this structure. It was thin walled in some areas and coursing across its cavity and particularly in the region of its orifice were numerous fine filmy trabeculations. This aneurysm was then removed. The left ventricular endocardium appeared normal in appearance but the endocardial surface of the aneurysm was white with fibroelastosis.

His postoperative course was uneventful except for a short episode of supraventricular tachycardia. A chest x ray and a ventriculogram done four years after surgery showed the area of the previous aneurysm to be thinned and bulging minimally but the left ventricle contracted well. When last seen at the age of 16 years the patient was asymptomatic, his weight was 50 kilograms and his height was 160 cm.

Case history 4. J. O. This child was admitted to Hennepin County Medical Center at the age of 13 months with a history of delayed development and poor use of the right side of his body. A few days prior to his admission to the hospital he had a seizure which was described as eyes deviating to the left with child becoming rigid. The patient was the product of a normal pregnancy and delivery with a birth weight of 6 pounds and 7 ounces. There were no neonatal problems. The growth and development were described as normal up to about six months of age when the mother noticed that he did not use his right upper or lower extremities well. After that his growth and development were delayed and he did not sit until the age of 13 months, had never crawled and used very few words.

His weight on admission at 13 months was 7.6



Fig 9 Case 4 Chest x ray in posteroanterior view demonstrates features similar to the ones seen in Case 1 *(Fig 1)* The bulge in the region of the apex is less dense than the rest of the heart The ventriculogram *(B)* in the same patient shows a large aneurysm in the left ventricle apical region The major coronary artery branches are normally distributed

kilograms with a height of 70 cm The pulse rate was 120 per minute with a respiratory rate of 36 per minute and his head circumference was 44 5 cm The child had equal but elevated blood pressures in his arms and legs averaging 140/80 mm Hg The neurological examination suggested bilateral Babinski sign sustained lower left knee jerk and no grasp The child did not respond to any verbalization or follow a light The cardiac examination revealed a Grade II/VI murmur along the left upper sternal border but the heart sounds were of normal quality The liver was 1 cm palpable below the right costal margin The chest x ray (Fig 9A) revealed a prominent cardiac apex and the electrocardiogram showed an axis of +70 degrees with a prolonged QRS interval and an intraventricular conduction delay with left ventricular hypertrophy ST and T waves were depressed in the left chest leads A left carotid angiogram revealed occlusion of the internal carotid artery and a hypoplastic extracranial portion of this artery A heart catheterization performed a few days later showed normal hemodynamics and ventriculography (Fig 9B) showed a 3 to 4 cm aneurysmal bulge at the apex of the left ventricle The opaque dye remained in the aneurysm through the study The proximal coronary arteries were visualized and appeared normal The pressure in the left ventricle was 120/6 8 mm

On cardiopulmonary bypass an ill defined left ventricular aneurysm was identified This structure was opened no clots were found and the entire aneurysm could not be removed since it involved both anterior and posterior papillary muscles

A second heart catheterization was performed about a month later and left ventriculography again demonstrated a 3 to 4 cm aneurysmal dilatation of the apex of the left ventricle in which the dye did not clear as rapidly as it did in the remainder of the left ventricle It was felt that there was persistence of the left ventricular aneurysm The child was then seen about five months after the surgery without any significant change in his findings About nine months after the surgery the mother found the child dead in bed A postmortem examination was not obtained

Discussion

Abbott[3] first described congenital aneurysm as diverticulum of the heart and these two terms

have frequently been used interchangeably Recently a distinction has been made between a congenital aneurysm and diverticulum of the heart The diverticulum is thought to be secondary to a developmental defect of the septum transversum[4] percursor of the diaphragm It is usually a smooth walled structure non contractile and involves the apex of the heart In addition defects of the pericardium diaphragm and abdominal wall in the midline of the body are present[5, 6] In contrast congenital aneurysm is a well demarcated out pouching of the ventricular wall[7] The wall of the aneurysm is usually muscular contractile and the lumen shows numerous trabeculae as seen at operation in our Case 3 Endocardium showing a variable degree of fibroelastosis and calcification in the wall has been reported The orifice of the aneurysm is usually close to the apex of the left ventricle but an increased incidence of congenital aneurysms with opening in the left ventricle just below the mitral valve has been described in Bantu[6] and Nigerian[1] patients

The muscular aneurysms typically arise from the left ventricle but an origin from the right ventricle cavity has been reported[12] Although ventricular aneurysms are mostly isolated defects Carter and associates[3] reported an aneurysm arising from the right ventricle in a patient with ventricular septal defect and pulmonic stenosis

Etiology The embryological basis for congenital aneurysm of the heart has been discussed by several authors [15] but there is no general consensus It is postulated that in fetal life the ventricular wall might give way at a point of weakness

The acquired causes of left ventricular aneurysm include origin of the left coronary artery from the pulmonary artery [6] blunt trauma to the chest[4] tuberculous or mycotic[19] myocardial infection postoperative cardiac surgery and mucocutaneous lymph node syndrome

Presenting signs and symptoms The patient with congenital ventricular aneurysm usually is asymptomatic and the defect is suspected if the cardiac silhouette is abnormal on chest x ray as it was in our first two patients An abnormal electrocardiogram symptoms of congestive heart failure and tachyarrhythmia may lead the patient to seek medical advice Some patients may be seen with neurological complications secondary to thromboembolic phenomena as was the case described by Vazquez and associates[21] and our fourth patient

Bacterial endocarditis and mitral regurgitation[22] may be the mode of presentation and the latter does not seem to be related to any specific etiology of the left ventricular aneurysm but is rather a function of time indicating a long standing lesion Most of the cases described have presented with sudden death due to rupture of the aneurysm[1, 15, 3] There are at least three reports in the literature of successful repair of a ruptured left ventricular aneurysm[23, 7] The reason for the rupture is not clear but it has been postulated to be due to the development of excessive pressure in the lumen of the structure The ventricular contraction that precedes the contraction of the wall of the aneurysm occludes the opening of the aneurysm in the left ventricular cavity and the subsequent contraction of the aneurysm is against a closed orifice

Diagnosis Provided it is known that malformation occurs the diagnosis can be supported by x ray fluoroscopy electrocardiography echocardiography[29] radioisotope scanning[3] and can be confirmed by ventriculography

A similar x ray picture can be produced by a pericardial cyst or a mediastinal tumor The electrocardiogram is usually normal in these two conditions while it is invariably abnormal though nonspecific in patients with congenital left ventricular aneurysms Experience with radioisotope scanning and echocardiography is as yet limited and ventriculography though invasive is the only means of definite diagnosis at this time As more experience is gained with the two dimensional echocardiogram this noninvasive procedure can be used not only to diagnose this lesion but also to follow its progression

Ischemic ventricular aneurysm secondary to anomalous origin of the coronary artery or mucocutaneous lymph node syndrome are poorly demarcated and can be easily differentiated

Natural history and treatment The natural history of congenital ventricular aneurysm is not known in asymptomatic children therefore the place for surgical treatment in asymptomatic cases with uncomplicated lesions is not known and a review of the literature does not give us a definite answer We elected to wait and watch our two asymptomatic children and operated on our two symptomatic patients The causes of symp

toms in our third patient could not be clearly related to the ventricular aneurysm

The treatment of choice with any of the above mentioned complications is surgical It is evident that surgical treatment may be difficult as there is no clear-cut demarcation between the ventricular and the aneurysmal tissue It is essential that the size of the ventricular cavity proper must be assessed to be adequate and the course of the coronary arteries must be well demarcated prior to surgical removal of the aneurysm

The authors wish to thank Janice L. Pearson for secretarial assistance and Jeanne D Olson and Alice A. Schwegman for technical help

REFERENCES

1. Telling, M., and Woller G H Excision of cardiac aneurysm Lancet 2 181 1961
2. Wang C H., Bland, E F., and White P D A note on coronary occlusion and myocardial infarction found postmortem at the Massachusetts General Hospital during the 20 year period from 1926-1945 Ann Intern Med. 29 601 1948.
3. Abbott M E. *In* Osler W., and McCrae T Modern Medicine ed. 2, Philadelphia, 1915 Lea & Febiger vol. 4 p 43
4. Cantrell, J R., Haller J A., and Ravitch M M A syndrome of congenital defects involving the abdominal wall, sternum, diaphragm pericardium, and heart Surg Gynecol. Obstet 107 603 1958
5. Skapinker S Diverticulum of the left ventricle of the heart. Review of literature and report of successful removal of diverticulum, Arch. Surg. 63 629 1951
6. Potts, W J DeBoer A. and Johnson, F R Congenital diverticulum of the left ventricle case report Surgery 33 301 1953
7. Treistman, B Cooley D A Lufschanowski, R., and Leachman, P D Diverticulum or aneurysm of left ventricle Am J Cardiol. 32 119 1973
8. Paronetto F and Strauss, L. Aneurysm of the left ventricle due to congenital muscle defect in an infant Report of a case with pathogenesis of associated endocardial fibroelastosis, Am J Cardiol. 12 721 1963
9. Dimich, I Steinfeld, L., and Baron, M Calcified left ventricular aneurysm in children Am J Cardiol. 23 739 1968.
10. Chesler E Tucker R B R and Barlow J B Subvalvular and apical left ventricular aneurysms in the Bantu as a source of systemic emboli. Circulation 35 1156 1967
11. Abrahams D G Barton C J Cockshott W P., Edington, C M and Weaver E J M Annular subvalvular left ventricular aneurysms. Q J Med 31 345 1962.
12. Cumming, G R. Congenital diverticulum of the right ventricle Am J Cardiol 23 294 1969
13. Carter J B., Van Tassel R A., Moller J H., Amplatz, K., and Edwards J E Congenital diverticulum of the right ventricle Association with pulmonary stenosis and ventricular septal defect Am J Cardiol. 28 478 1971
14. Sweer A. J., Mauss, I H., and Rosenblatt P Congenital diverticulosis of left ventricle Am J Dis Child. 79 111 1950
15. Drennan M R Van der Vijver G T., and Pearston C B A diverticulum of the human heart J Med Assoc S Afr 2 58 1928
16. Bland E. F., White P D and Garland J Congenital anomalies of the coronary arteries Report of unusual case associated with cardiac hypertrophy Am Heart J 8 787 1933
17. Joachim H., and Mays A T A case of cardiac aneurysm probably of traumatic origin Am Heart J 2 682, 1927
18. Jones, K P., and Tilden K Tuberculous myocardial aneurysm with rupture and sudden death from tamponade review of literature and report of case Hawaii Med. J 1 295 1942.
19. Pirani, C L. Erosive (mycotic) aneurysm of the heart with rupture Arch Pathol 36 579 1943
20. Robinson H B., and Donahoo J S Postoperative aneurysms of the heart. Case report and review of the literature J Cardiovasc Surg 18 181 1977
21. Franco-Vazquez, S., Sutherland R D., Fowler M., and Edwards, J E Congenital aneurysm of left ventricular base Chest 57 411 1970
22. Gueron M., Hirsch, M., Opschitzer I., and Mogel, P Left ventricular diverticulum and mitral incompetence in asymptomatic children Circulation 53 181 1976
23. Burn C G., Hollander A G and Crawford, J H Rare cardiac aneurysm in a child Am Heart J 26 415 1943
24. Meyersohn J., and Schiffer J Rupture of a congenital aneurysm of the left ventricular apex Chest 63 838 1973
25. Pettersson G., and Bergstrom T A case of ruptured diverticulum of the left ventricle with hemopericardium in a neonate treated successfully by surgery Scand. J Thorac Cardiovasc Surg 3 203 1969
26. Bjork, V K. Congenital left ventricular aneurysm, Thorax 20 190 1965
27. Johansson, L., Michaelsson, M., and Sjogren S Congenital left ventricular apical aneurysm Scand J Thorac Cardiovasc Surg 10 135 1976
28. Lowe, J B Williams, J C P Robb D., and Cole D Congenital deverticulum of the left ventricle Br Heart J 21 101 1959
29. Petersen J L., Johnston W Hessel, E A and Murray J A. Echocardiographic recognition of left ventricular aneurysm Am Heart J 83 244 1972
30. Meek, D C., Brown D W Schmock C L., and Blount S G Demonstration of ventricular aneurysms by radioisotope scanning Radiology 85 856 1965

Transverse midventricular disruption after mitral valve replacement

B Woodfin Cobbs Jr M D *
Charles R Hatcher Jr M D **
Joseph M Craver M D **
Ellis L Jones M D ** *
Charles W Sewell M D *** *
Atlanta Ga

Between 1975 and 1977 while the risk of coronary bypass and aortic valve surgery in our experience was 1 1% and 3 5% respectively our hospital mortality rate for mitral valve replacement remained 7 5% There were 294 patients including 48 with multiple replacements and 18 with mitral regurgitation resulting from coronary disease The major cause of death was a newly recognized problem Transverse midventricular disruption (TMD) was found in seven autopsied cases clinically suspected in three others and successfully repaired in one case Clinical presentations were (1) refractory left ventricular dilatation and failure appearing at the time of removal from bypass or soon afterwards (four cases) (2) severe myocardial failure closely followed by midventricular rupture Type II of Treasure and colleagues (two cases) (3) completely unheralded midventricular rupture 6 hours and 4 days postoperatively (two cases) The pathology in all three types was basically the same In an effort to understand this complication we closely analyzed our operative techniques and made careful pathological studies Because fixation petrifies myocardial consistency and hides potential planes of movement gross observations were usually recorded on movie film Microscopically both transverse and longitudinal sections were made the latter providing the most important information

The first question was whether the problem entirely new Review of earlier data suggested that the incidence had at least increased though incomplete forms (one half of our group) might have been previously missed Thus we considered the obvious changes which had occurred during the study period These included an older patient group the introduction of the Hancock valve and the use of potassium and cold induced cardioplegia for myocardial protection [2, 3]

Incomplete rupture has been known to produce false aneurysm but has not been recognized as a cause of the acute and profound left ventricular failure which occasionally follows mitral valve replacement Complete rupture is a well known complication comprising 2% of Bjork and associates series and 0 5% of the series of Zacharias and co workers [6] The majority have occurred at the mitral annulus which was not involved in any of our group The midventricle was thought to be the site of rupture in only 12 of the 34 previously reported patients [1, 4, 10] Explanations offered for this problem have included (1) cutting too deep a plug and buttonholing the ventricle during excision of the papillary muscle in a fragile atrophic mitral ventricle [1, 4, 8] (2) dissection of blood into the papillary muscle wound (3) trau

From the Dep rtments of Medicine (C rdiology) Thoracic and Card o-vascular Surgery nd Pathology Emory Un ersity School of Medi cin and Emory University Hosp tal, Atlanta Georgia

Received f r publicat on June 6 1979

Accepted for publication Aug 27 1979

Reprint requests B Woodfin Cobbs Jr M.D Emory Uni ersity Clinic Atlanta Ga 3032

Professor of Med cine (Cardiology) Emory Uni ersity School of Med cine Atlanta Georgia

Profess r and Chief Thora ic and Card ovascular Surgery Emory Uni ersity School of Medicin Atlanta Georgia

Assistant Professo Thoracic and Cardiovascul r Surgery Emory Uni ersity School of Medicin Atlanta Georgia

Associate Pr fessor Thoracic and Cardiovascul Surg ry Emory Un rs ty School of Medici Atlanta Georgia

Assistant Professor of Pathology Emory University School f Medicine Atlanta Georgia

0002-8703/80/010033 + 18$01 80/0

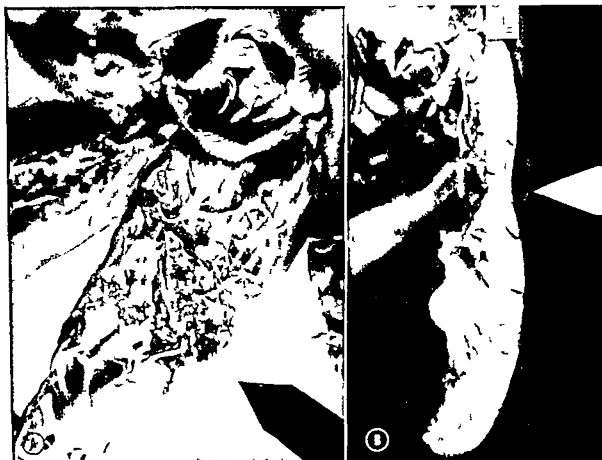


Fig 1 Case 1 *A* Death 3 days after TMD The macerated and thinned area above the posterior papillary site was actually two partial thickness tears which could be re approximated restoring full thickness of the wall. *B* Lateral view of thinned area Hancock struts are well above the tear

ma from apical venting [5] (4) epicardial adhesions [5] (5) impingement of a valve strut [9] (6) intrinsic myocardial disease [1] and (7) interruption of continuity between papillary muscle and mitral annulus Our findings revised and augmented this list suggesting that an interplay of factors may be necessary to produce TMD

Case reports

Case 1 A 61 year old woman with rheumatic heart disease had been symptomatic for 12 years with atrial fibrillation episodic pulmonary edema and progressive right sided failure Cardiac catheterization showed a mitral gradient of 20 mm Hg moderate mitral regurgitation and huge left atrium The cardiac index was 2 8 L/min/M the left ventricular ejection fraction was 60% with an end diastolic pressure of 5 mm Hg The coronaries were normal At operation in December 1975 there was severe chordal resorption so that the papillary muscles were pulled close to the mitral annulus The anterior leaflet was in abnormally high position and perpendicular (rather than normally tangential) to the plane of its chordae The patient was maintained on cardiopulmonary bypass at a temperature of 28° C Local cooling with iced saline was also used With the heart fibrillating the aorta was cross clamped for three periods totaling 36 minutes The mitral valve was replaced with a No 29 Hancock prosthesis Venting was accomplished by means of a Foley catheter placed transmitrally no suction tip ever entering the ventricle Defibrillation was uneventful But a few minutes after the heart was allowed to fill it dilated and never pumped satisfactorily thereafter ST elevation suggesting high lateral myocardial infarction persisted for 24 hours until left bundle branch block and pulmonary edema appeared on the second postoperative day Despite increasing

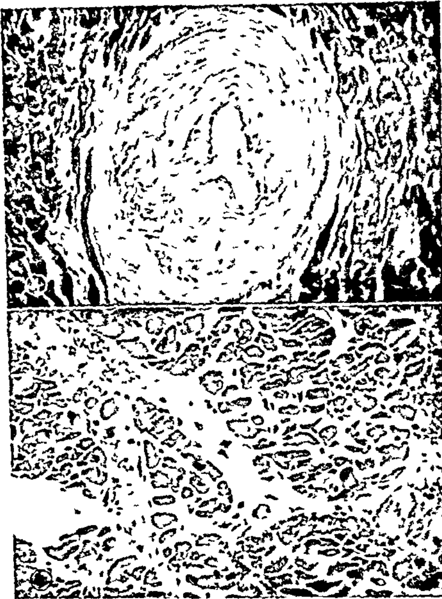


Fig 2 Case 1 A Obliterative intimal changes involved most arteries in the papillary muscles and their root systems, but spared the adjacent ventricle even the area of the tear B Widened spaces between transversely running fibers. Marked sarcolysis with many myocardial nuclei lying free This longitudinal section was taken 0 7 cm above the tears, where the muscle grossly appeared normal.

pharmacologic support and use of the balloon pump peripheral pressures fell and the left atrial pressure hovered at 30 mm Hg Death occurred at 72 hours At postmortem examination the heart weighed 460 gm the coronaries were free of atheroma and none had been ligated The heart had not ruptured But the left ventricle which was 1 1 cm in thickness at the base abruptly thinned just above the papillary muscles to as little as 0 5 cm in a transverse band 1 4 cm wide and 4 cm long Inspection of the endocardial surface showed two roughly parallel partial thickness tears each of which was opened out flat leaving a zone of intact endocardium in between (Fig 1) Full thickness of the myocardium and endocardial continuity could be restored by pushing together these myocardial pleats But without being held they reverted to their old open flat state implying that the separation had been present for some time probably since operation

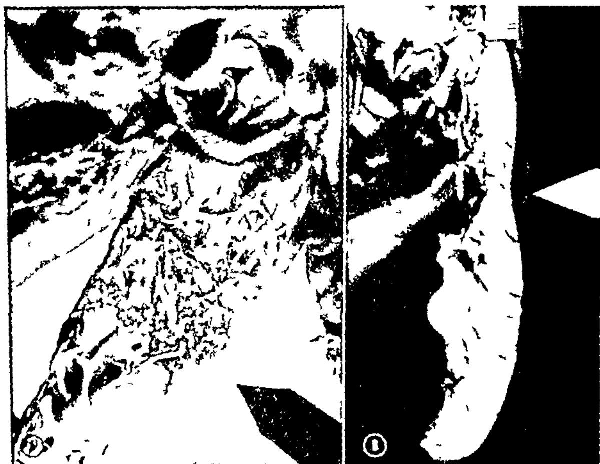


Fig 1 Case 1 A Death 3 days after TMD The macerated and thinned area above the posterior papillary site was actually two partial thickness tears which could be re approximated re toring full thickness of the wall B Lateral view of thinned area Hancock struts are well above the tear

ma from apical venting[5] (4) epicardial adhesions[5] (5) impingement of a valve strut[6] (6) intrinsic myocardial disease[1] and (7) interruption of continuity between papillary muscle and mitral annulus Our findings revised and augmented this list suggesting that an interplay of factors may be necessary to produce TMD

Case reports

Case 1 A 61 year old woman with rheumatic heart disease had been symptomatic for 12 years with atrial fibrillation, episodic pulmonary edema and progressive right sided failure Cardiac catheterization showed a mitral gradient of 20 mm Hg moderate mitral regurgitation and huge left atrium The cardiac index was 2 8 L/min/M² the left ventricular ejection fraction was 60% with an end diastolic pressure of 5 mm Hg The coronaries were normal At operation in December 1975 there was severe chordal resorption so that the papillary muscles were pulled close to the mitral annulus The anterior leaflet was in abnormally high position and perpendicular (rather than normally tangential) to the plane of its chordae The patient was maintained on cardiopulmonary bypass at a temperature of 28° C Local cooling with iced saline was also used With the heart fibrillating the aorta was cross clamped for three periods totaling 36 minutes The mitral valve was replaced with a No 29 Hancock prosthesis Venting was accomplished by means of a Foley catheter placed transmitrally no suction tip ever entering the ventricle Defibrillation was uneventful But a few minutes after the heart was allowed to fill it dilated and never pumped satisfactorily thereafter ST elevation suggesting high lateral myocardial infarction persisted for 24 hours until left bundle branch block and pulmonary edema appeared on the second postoperative day Despite increasing



Fig 4 Case 3 *A* A double transverse tear leaves a large pseudo trabecula and extends forward into the septum. The lower tear touches the margin of the closely cut posterior papillary stump *(P)* (here pulled forward and seen from above) Endocardium medial to the top of the anterior papillary stump *(A)* has apparently been surgically nicked Ventricular wall "hyperextended" to show the full extent and depth of the tear *B* Longitudinal section of papillary muscle showing patchy often cross-banded fibrosis perpendicular to the fiber axis and attributed to "stretch myocardiopathy" as the result of severe chronic mitral prolapse In many sections the fibrosis was more diffuse

site[1] But internally there was an extensive 4 5 cm endomyocardial tear beginning 0 2 cm above the tip of the anterior papillary muscle extending transversely along the free wall of the ventricle and passing 1 cm above the posterior papillary muscle into the septum Both papillary muscles were intact and microscopically showed no significant abnormalities The closest Hancock strut was 1 2 cm from the tear Anteriorly the plane of the surgical incision of the chordae tendineae was in line with the break in the adjacent myocardium with only a few millimeters clearance suggesting the possibility of an inadvertent surgical nick In many parts of the lesion blood had dissected almost completely through the ventricular wall restrained only by the thin external longitudinal muscle layer which had parted in the area of complete rupture Microscopic examination indicated that the tear had developed mostly along a natural plane of transverse cleavage vertical trabeculation above the lesion was rather well developed but virtually ended just above the papillary muscles where the trabecular roots turning as much as 90 degrees plunged outward through the thick middle layer of circumferential muscle bundles (Fig 3) The tear generally followed the inferior margin of these "plunge fibers" with no cellular reaction although some inner parts were lined with fibrin suggesting that the process may have begun earlier than was clinically apparent There was also considerable microscopic hemorrhage along

plunge fibers as much as 1 4 cm above and 0 8 cm below the tear

Case 3 A 69 year old woman found to have a heart murmur on routine examination developed congestive heart failure and atrial fibrillation 3 years later At cardiac catheterization the wedge pressure was 23 mm with a V wave of 30 and a very large left atrium The left ventricular end diastolic pressure was 12 Mitral regurgitation appeared severe with a regurgitant fraction of 0 42 despite this unloading the left ventricular ejection fraction was only 40% The cardiac index was 1 4 L/min/M The coronary arteries appeared normal There was very severe mitral annular calcification At operation in May 1976 both leaflets were aneurysmal myxoid and obviously chronically prolapsed—judging from the perpendicularity of chordae to the leaflet plane While the chordae were long none was broken This appeared to be an example of severe chronic mitral prolapse leading to calcification and dilatation of the mitral annulus with the mitral regurgitation probably aggravated by selective papillary muscle failure [11] The patient was maintained on cardiac bypass at 28° C aortic cross clamping for 45 minutes was required Intra aortic perfusion of potassium solution and both epicardial and endocardial cooling with iced saline were employed for myocardial protection The left ventricle was vented transmitrally with a soft plastic cannula *and no suction tip was ever placed in the ventricle* As cardiac bypass was diminished the patient s left ventricle failed to muster enough pressure to open the aortic valve and she could not be weaned from the pump At postmortem examination the heart was unusually flabby and weighed 490 gm with left ventricular hypertrophy There was no external sign of rupture but a complex and deep endomyocardial tear (Fig 4 *A*) spiraled 6 5 cm posteriorly from a point close to the base of the anterior papillary muscle along the free wall of the left ventricle and thence into the septum where it arched superiorly A lower tear began in the posterior papillary groove and continued even farther into the septum where it neatly divided the smooth and trabeculated portions leaving a furrowed surface of exposed muscle bundles Posteriorly the tears produced a large free standing bundle which resembled an elegant anatomic dissection Here vertical trabeculation was virtually absent and the lesions appeared to follow natural circumferential creases Longitudinal compression closed the cleavage planes completely virtually concealing them Hyperextension of the ventricle opened the tears and revealed several fine branches at both ends which could be extended with minimal tension It looked as though the heart had simply come apart Microscopically there was evidence of a diffuse process dilatation and focal rupture of intramural venous sinusoids and separation of transverse fiber bundles throughout the free wall of the left ventricle and the involved part of the septum the findings sometimes obvious as much as 2 cm basal to the tear Also 1 to 2 mm pools of hemorrhage were noted along the inner walls of the papillary muscles and around the intramural extensions of their root systems Although the papillary muscles appeared grossly normal microscopically on longitudinal sections there was severe predominantly cross banded fibrosis with no significant involvement of the myocardium elsewhere (Fig 4 *B*) The nearest distance from valve strut to tear was 1 8 cm Posteriorly the lower tear was directly in line with the stump of the posterior papillary muscle which had been resected very close to the ventricular wall (Fig 4*A*) While it seemed possible that a minor surgical nick had opened a natural plane of cleavage this seemed an insufficient explanation for the extensive upper tear or the diffuse microscopic lesions *A portion of the anterior papillary muscle* had also been closely resected and in the immediately adjacent ventricular wall there was a superficial cut 0 8 cm long which however did not connect with any part of the tear

Case 4 A 72 year old male was asymptomatic and normotensive until 6 weeks before admission when after a febrile illness he developed pulmonary edema and a pansystolic murmur Temporary pacing was used because of complete heart block Upon admission he was in sinus rhythm with a blood pressure of 110/80 a Grade III apical pansystolic murmur and a loud premature S_3 heart sound After the administration of diuretics the neck veins were normal but the chest x ray showed interstitial pulmonary edema and marked cardiomegaly At catheterization the pulmonary artery pressure was 80/28 There was severe mitral regurgitation associated with marked annular dilatation and calcification The left

ventricular end diastolic pressure was 13 rising to 32 after contrast medium injection Cardiac index was 2 1 L/min/M The ejection fraction appeared to be fair Coronary arteries were normal The ECG showed right bundle branch block with a PR interval of 0 24 seconds At surgery in June 1976 a No 33 Hancock valve was inserted and a permanent epicardial pacemaker was left in place There was rupture of two chordae to the medial portion of the middle scallop of the posterior leaflet Both leaflets were aneurysmal thickened and severely prolapsed with stiffly perpendicular chordae attesting to the chronicity of the process Microscopically there was severe myxoid degeneration The severity of the mitral regurgitation appeared as much due to the chronic leaflet disengagement papillary muscle failure and annular dilatation as to the moderate recent chordal rupture[11] A total of 67 minutes of aortic occlusion time was needed during which the heart was protected with local cooling Potassium cardioplegia was not used No suction tip ever entered the left ventricular cavity which was vented transmitrally with a soft plastic tip Postoperatively there was immediate hemodynamic improvement The heart came off bypass requiring no inotropic support The patient s course was quite smooth until 4½ days postoperatively when feeling well and sitting in his chair he suddenly exsanguinated At postmortem the left thorax and mediastinum were full of blood The heart weighed 750 gm with marked thickening and dilatation of the left ventricle and atrium and no coronary ligature The area of the epicardial break was initially overlooked being only a small vertical slit 0 4 cm long The papillary muscles though quite large were grossly unremarkable Yet longitudinal sectioning revealed diffuse fibrosis which in less severe areas was of the cross banded type and largely spared the underlying ventricle[3] Just above the papillary muscles there were two transverse tears totalling 6 cm in length neither less than 2 cm from the nearest Hancock strut (Fig 5) The deepest tear almost avulsed the anterior papillary muscle followed plunge fibers from the papillary groove through to the epicardial surface and was responsible for the external rupture About 6 mm of intact trabeculation separated this from a more superficial transverse tear just above the tip of the posterior papillary muscle Here on quick



Fig 5 Case 4 Sudden TMD 4½ days after mitral valve replacement. Torn surfaces fresh glistening without fibrin or necrosis. Discrete tears above both posterior *(P)* and anterior *(A)* papillary muscles with 6 mm. intact trabeculation between Anteriorly the ventricle separated just beneath a broad sheath of plunge fibers which directed the tear through to the epicardium

inspection it was easy to mistake exposed muscle bundles for normal trabeculae Some apparently sturdy vertical trabeculae had been broken but at their bases where they terminated in the tear area Both papillary muscles were free standing none had been resected and there was wide clearance from the adjacent left ventricular wall Microscopically localized to the posterior papillo ventricular groove below the line of the tear there were small pools of edema and sarcolysis the latter possibly dating back 4½ days to the time of surgery The torn surfaces themselves showed no necrosis and very little fibrin deposition implying that the break had been sudden and agonal Thus it appeared that ruptured chordae had complicated the course of cardiomyopathy associated with long standing mitral prolapse and its secondary effects on the mitral



Fig 6 Case 5 TMD in a patient with rheumatic heart disease The Hancock struts are unusually close to the edge of the tear Surgical repair was unsuccessful because only the outer layers were approximated and then only in the area of the external break

annulus and papillary muscle[1] Perhaps anlage for TMD in this case may have resembled the pools of fiber separation and sarcolysis seen in the papillary groove But the delay in onset of the tear the lack of necrosis or of any structurally impressive lesions dating back to the time of surgery, and the absence of any visible source of trauma implied some sort of cumulative process

Case 5 A 70 year old woman with a childhood history of rheumatic fever had been diuretic dependent for 12 years and nearly bedridden for one year On examination she had mitral systolic and diastolic murmurs a brief blow of aortic insufficiency isoelectric atrial fibrillation and a huge left atrium Although she had been given diuretics to free her from edema the neck veins had large V waves suggesting tricuspid incompetence Angiographically the left ventricular size was only moderately increased The ejection fraction was 48%, with severe mitral and a trace of aortic regurgitation The coronaries showed minor luminal irregularities The pulmonary artery pressure was only 28/10 probably as a result of the giant left atrium and low output There was a 4 to 5 mm mean diastolic gradient over the tricuspid valve and marked venous unsaturation At surgery in July 1976 the patient was maintained at 25° C and the heart further cooled with iced saline The mitral leaflets were fused and retracted the papillary muscles were almost absorbed into the valve Replacement was with a No 31 Hancock prosthesis The severe tricuspid leak was corrected by annuloplasty At one point a suction tip introduced into the left ventricle was inadvertently wedged into the papillary groove Yet the patient did quite well was defibrillated with one countershock and came off bypass without pharmacologic support Cardiac output increased from 2½ to 4½ liters with a left atrial pressure of 15 mm Hg Twenty minutes later during closure of the sternum the heart suddenly slowed and distended Lateral ST elevations were noted on the ECG but no air was seen in the coronaries Manual cardiac massage was begun Within a few minutes copious bleeding was noted from a tear in the left ventricular surface which appeared to be 1 5 cm below the atrioventricular groove near the anterior papillary site Repair necessitated ligature of an anterior obtuse marginal coronary artery Thereafter the ventricle never pumped adequately The patient lived for 2 days with intensive hemodynamic support her ECG showing lowered voltage and marked lateral ST elevation X ray evidence of pulmonary edema did not develop but volume loading raised filling pressures without affecting systemic pressure Reexploration excluded tamponade and showed a virtually akinetic left ventricle In the last 24 hours right bundle branch block developed Shortly before death thoracotomy drainage increased sharply At autopsy there was a massive hemomediastinum with 800 gm of clotted blood The Hancock prosthesis appeared to be well seated The heart weighed 500 gm with no critical coronary lesions An unusually straight and deep endomyocardial tear 5 cm long



Fig 7A. Case 6. TMD in a patient with chronic mitral prolapse. A misaligned Hancock valve may have left V shaped on the septum *(V)* but there are discontinuous tears in each papillary groove with 1.2 cm of intact vertical trabeculation between. The deepest lesion is the area of apparent erosion above the anterior papillary muscle *(A)* which has been pulled forward. The posterior tear is hidden behind the muscle *(P)*. Both tears were initially missed.

extended transversely from 0.6 cm above the posterior papillary tip near the septum to a corresponding point above the anterior papillary site where the area of ventricular repair was aneurysmal (Fig 6). The left ventricle was focally thinned to 0.4 cm for the entire length of the lesion. The papillary muscle tips had been conservatively resected but at a point quite close to the line of the tear. In the anterolateral wall there was fresh myocardial infarction related to the surgically ligated anterior obtuse marginal artery. Thus detailed microscopic studies were done only near the posterior papillary muscle. The surface of the tear was lined with fibrin but there was very little necrosis. The papillary stump showed a great deal of fiber separation and sarcolysis. In the basal ventricle even 1 cm posterior to the lesion thin sheets of hemorrhages following the line of dilated venous sinusoids extended almost to the epicardial surface, these lesions having no direct connection with the tear itself. Vertical trabeculation was quite defective in the entire area but it was not possible to identify any obvious plane of natural cleavage. At the posterior papillary site the Hancock strut came within 2 mm of the edge of the tear and the inflow tract appeared too small for the No. 31 prosthesis. Thus it seemed quite possible that the valve strut had initiated the tear although there were no discrete strut marks and the lesion appeared too extensive to have been caused entirely by focal trauma.

Case 6. A 76-year-old male known to have a "leaking valve" and palpitations for 30 years suddenly developed severe congestive failure and was found to have an apical pansystolic murmur, a closely spaced S_3 gallop, and atrial fibrillation. Cardiac catheterization after diuresis showed severe mitral regurgitation and dilatation of the left ventricle with an ejection fraction of 50%, an end diastolic pressure of 12, and no significant coronary disease. The pulmonary wedge V wave was 24, the PA pressure was 32/16, and the cardiac index was 2.0 L/min/M². At surgery in March 1977 the mitral annulus was large, both leaflets were aneurysmal with ruptured chordae to the midportion of the middle scallop of the posterior leaflet. Pathologically there was severe myxoid degeneration and marked perpendicularity of chordae to both leaflets. It seemed probable that the patient had mildly symptomatic mitral prolapse for many years before rupturing chordae



Fig 7B Case 6. Wide separation of transverse fiber bundles even in the untorn segment, decremental toward the base A residue of proteinaceous fluid in the widened spaces suggested that they were not fixation artifact.

as the result of chronically increased mitral stress. A No 33 Hancock valve was inserted Myocardial protection was afforded by profound endocardial and epicardial hypothermia as well as by potassium cardioplegia maintained during a 28-minute period of aortic cross-clamping The procedure was uncomplicated After defibrillation the patient went into sinus rhythm with excellent ventricular function Ten minutes later the rate slowed requiring atrial pacing Then with the chest nearly closed a ventricular ectopic beat on the T wave initiated ventricular fibrillation and severe acute dilatation Although defibrillation was done almost immediately the ventricle never again contracted effectively and could not be brought off bypass even with the use of the intra aortic balloon At postmortem the heart on external examination seemed intact It weighed 420 gm. and was unusually flabby There was a separate transverse endocardial tear in each papillary muscle groove especially long and deep anteriorly The lesions were largely concealed until the papillary muscles were pulled forward or the wall was hyperextended (Fig 7A) The two tears were directly in line with each other and were separated by 1 cm of intact vertical trabeculation which was sturdy and well rooted toward the apex. The surfaces of the lesions were irregular because of exposed muscle bundles The prosthesis was apparently rather wide for the ventricle and had been mounted so that one of its struts faced the septum where there was a superficial V-shaped endocardial break This however did not quite match the position of the strut At its apex the V communicated with the tear in the posterior papillary groove The distance from strut to tear was 0 5 cm posteriorly and 1 2 cm anteriorly Thus while strut impingement might have initiated the posterior tear there must have been a different explanation for the independent and deeper anterior lesion Microscopically there was marked separation of the circumferential muscle bundles greatest at the level of the papillary muscle and decremental toward the mitral annulus (Fig 7B) These changes and the extreme flabbiness of the heart resembled findings in Case 3 whose mode of death was similar The papillary muscles also showed cross banded fibrosis and intimal proliferation of small arteries the latter not as severe as in Case 2

Case 7 A 52 year old man suddenly developed substernal chest pain pulmonary edema shock, and a Grade II decrescendo apical systolic murmur in August 1977 Because of the absence of QRS abnormality the diagnosis of ruptured chordae was suspected Cardiac catheterization showed occlusion of the circumflex trunk but excellent movement of the entire left ventricular wall with an ejection fraction of 70% There was massive mitral regurgitation but little enlargement of the left atrium The left ventricular end-diastolic pressure was 15 rising to 21 after angiography Surgery done within 4 days of the chest pain showed that a necrotic 1 cm by 1 cm by 0 5 cm tip of the anterolateral papillary muscle had ruptured Very likely acute ischemic loss of papillary function had resulted in sudden severe mitral prolapse which increased stress on the underlying muscle[1] and contributed to rupture The valve was replaced with a No 27

Hancock prosthesis and the posterior lateral obtuse marginal artery was grafted Potassium cardioplegia and local epicardial cooling were used during the 54 minute period of aortic cross-clamping Decompression was by transmitral venting No suction tip ever entered the ventricle Off bypass the patient did very poorly despite heavy catecholamine support and the intra aortic balloon pump The ECG showed much decreased QRS voltage and marked lateral ST elevation which did not evolve Death occurred 2 days later At postmortem examination there was complete occlusion of the circumflex trunk but the graft was patent and the other coronaries were unremarkable The heart weighed 780 gm There was grossly visible infarction of the anterior papillary stump and a 1 5 cm area adjacent to the mitral annulus both thought to be about 1 week old Microscopically there were also scattered foci of posterior papillary and subendocardial necrosis A superficial transverse tear 6 cm long but only 0 2 to 0 4 cm deep extended along a line 0 2 cm above the anterior papillary muscle beyond a point 1 2 cm above the posterior papillary tip (Fig 8A) It was coated with fibrin but did not involve infarcted muscle The tear appeared to have developed in a normal transverse crease (in an area with almost no vertical trabeculation) and to have followed a line of natural fiber cleavage which microscopically proved to be a venous sinusoid Although the lesion appeared shallow there was microscopic evidence of TMD in a wide area

1 From the apex of the tear the sinusoidal cleavage plane continued branching outward almost to the epicardium In this unrealized part of the lesion the vascular channel was focally dilated and broken with loss of endothelium and microhematomas invading adjacent muscle where bundles and even individual fibers were separated and there was focal sarcolysis

2 As much as 1 cm above the visible tear and roughly parallel to it streamer like perisinusoidal hematomas from dilated vascular channels penetrated the myocardium suggesting the potential for other breaks similar to the gross lesion (Fig 8B)

Case 8 A 64 year old woman in December 1977 had tight severely symptomatic mitral stenosis but good left ventricular function with an ejection fraction of 65% and a diastolic pres-



Fig 8A Case 7 TMD after replacement of the mitral valve for rupture of the anterior papillary muscle in coronary artery disease The shallow obliquely coursing tear follows a natural endocardial crease in an area of defective vertical trabeculation Though coated with fibrin it was easily missed until the heart was hyperextended.

sure of 8 mm Hg At surgery the mitral orifice was 1 0 by 0 4 cm The valve was contracted intra annular and diaphragm like with severely shortened chordae tendineae Very conservative resection was done leaving the papillary muscles full length Potassium cardiac arrest was used and the heart was locally cooled with iced saline A No 27 Hancock valve was inserted although it was felt to be a snug fit Venting of the left ventricle was accomplished through a soft catheter tip placed transmitrally As the vent was removed after defibrillation the initial contractions appeared normal but in 1 minute the heart abruptly dilated as ST elevation developed in the lateral and later in the inferior leads A careful search showed no air in the coronaries. TMD was

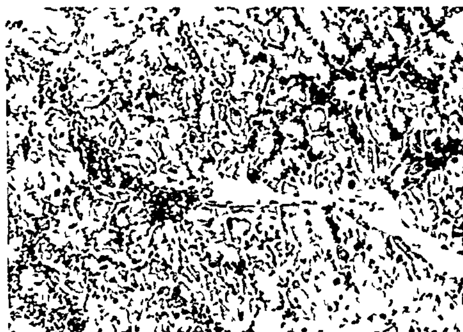


Fig 8B Case 7 One of many widened and ruptured venous sinusoids 0 5 cm deeper and 1 cm above the gross lesion

at once suspected because of the acute unaccountable power failure and the ST changes Venting was reinstituted but external massage was not used When bypass was finally discontinued an hour later the heart immediately ruptured from a 1 5 cm longitudinal slit in the posterior wall beginning 2 cm below the AV groove near the posterior papillary site With the *knowledge from previous anatomical studies that* the internal disruption was much more extensive and perpendicular to the exit wound the surgeon used deeply placed sutures and continued the repair 4 cm laterally as far as the approximate position of the anterior papillary muscle He ended by sewing the posterior pericardium and a knitted Dacron patch like a tamponading tent over about one third of the posterior ventricular wall fortunately sparing major coronary branches Even with the aortic balloon and intensive pharmacologic support there was great difficulty in weaning the patient off cardiac bypass For the first week postoperatively she was dependent on 1 1 balloon pumping and intensive pharmacologic support The ST elevations gradually cleared over a 60 hour period There were never any ECG changes of transmural myocardial infarction The echo indicated severe global hypokinesis of the left ventricle confirmed by a sector scan done 1 year later The patient remains in severe chronic heart failure

Summary of anatomic findings

Despite considerable variation in the depth of the tear lesions in the seven autopsied cases were remarkably similar and basically the same regardless of whether the heart had ruptured The *endocardial break always involved the free wall of* the left ventricle at or not far above the papillary sites and extended 4 to 6 cm circumferentially sometimes into the posterior septum The orientation of the lesion was generally transverse but often it spiraled somewhat upward higher posteriorly in general following the line of circumferential muscle bundles which comprise the bulk of the left ventricular wall In two cases the lesion tore deeply into the proximal groove between the papillary muscle and ventricle The break was often at least partly concealed pulling the papillary muscles forward or hyperextending the ventricle separated the planes of cleavage In two cases there were parallel tears in one instance dissecting out a large band of the spiral cardiac musculature In the other patient who survived partial rupture for 2 days the nature of the problem was not immediately obvious above the papillary muscles there was a zone of circumfer

ential thinning apparently partly denuded of intima yet intimal continuity and full thickness of the wall could be restored by folding the pleat like tears back together again In two patients who died in the operating room the cardiac muscle was unusually flabby and edematous so that the tear could be easily extended with minimal tension In five cases a deep and extensive tear was restrained in some areas only by the thin external longitudinal muscle layer Eventual rupture (in three cases) parted these fibers hence the exit was always vertical and perpendicular to the interior lesion

The preoperative lesions varied

1 A rheumatic diaphragm like valve with an abnormally high anterior leaflet chordal resorption and resulting stricture of the inflow tract (four cases)

2 Severe chronic mitral prolapse (three cases with chordal rupture in two)

3 Coronary artery disease with rupture of the anterior papillary tip (one case)

As we have previously pointed out disengagement of the leaflets particularly an abnormally high position of the anterior leaflet (removing the normal boundary between inflow and outflow tracts of the left ventricle) probably greatly increases sail traction on the papillary muscles and their ventricular attachments ' All patients except Case 7 showed abnormal perpendicularity of chordae to leaflets the commonest anatomical expression of chronic mitral disengagement The three patients with chronic mitral prolapse all had distinctive cross banded papillary muscle fibrosis findings not uncommon in older persons with long standing mitral valve prolapse and possibly due to stretch myocardiopathy or microbreakage of the muscle in a plane perpendicular to the fiber axis and to the stress applied ' The lesions tend to be perivascular (Fig 4 *B*) and could be due partly to capillary leaks In one patient (one rheumatic and one myxoid) the papillary muscles showed unusual obliterative disease of the small coronaries (Fig 2 *A*) perhaps also attributable to chronic trauma

While chronic abnormalities were common in the papillary apparatus the actual break occurred in the proximal myocardium through apparently healthy muscle with little if any necrosis even in patients who survived several

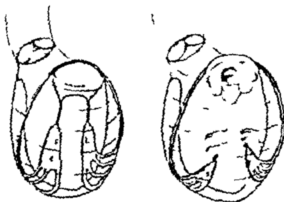


Fig 8 Schema of the "untethered ventricle" theory After mitral valve replacement in both systole and diastole there is abnormal longitudinal traction on the left ventricular endocardium which sometimes separates along natural lines of cleavage or foci of minor trauma.

days In five cases it was possible to show that the tear developed along natural lines of cleavage (1) venous sinusoids (2) points at which the roots of trabeculae carnae plunge through the ventricular wall (3) transverse creases in areas of absent or scanty trabeculation When vertical trabeculae were broken they were usually rooted in the area of the tear In control hearts considerable variation in the amount of vertical trabeculation above the papillary sites has been noted In some cases most of the longitudinal musculature of the endocardium is diverted into the mitral apparatus and even when present is rooted loosely or just above the papillary muscles not arranged to withstand much longitudinal stress The two patients with the best developed vertical trabeculation between the two papillary sites (Case 4 and Case 6) had separate tears with sparing of the areas where trabeculation continued uninterrupted toward the apex

Microscopically in many cases there was some evidence of transverse fiber disruption at some distance from the tear—the process usually decremental toward the base These accessory lesions consisted variously of (1) dilated fractured venous sinusoids (2) hemorrhages along plunge fibers (3) wide separation of transversely running muscle bundles and sometimes of individual fibers (with sarcolysis in those who survived for as much as 2 days) Foci of hemorrhage were also common in the papillary roots Case 7 showed

that mid ventricular disruption even when apparently superficial (and easily overlooked) could be quite long and circumferential with microscopic evidence of a more diffuse process

This aggregate of observations implied that TMD might be associated with abnormal myocardial stretching especially in the long axis of the heart

Discussion

Clinical recognition of TMD may seem all too simple once complete rupture has occurred But even here it must be differentiated from annular separation (Type I of Treasure and colleagues[1]) with which we suspect it has been confused Incomplete rupture more difficult to recognize is manifest by the sudden loss of effective left ventricular contraction usually soon after the completion of bypass Coupled with this may be ECG changes suggesting acute high lateral and even inferior infarction These findings should make the surgeon look carefully for coronary air embolism before diagnosing TMD The ST changes may be due to compression of adjacent branches of the circumflex coronary artery by the intramural hematoma But we think they are more likely caused by the pressure of dissected blood against the electrically active outer myocardial layer The fact that ST segments can remain focally elevated for nearly 3 days (Case 8) and finally return to normal without QRS abnormalities of infarction favors the second possibility

In trying to decipher TMD we considered a number of possible causes While several factors seem important it appeared that a combination was usually required The first recognition of the lesion in 1975 and its considerable incidence in the next 18 months appeared to be an important clue The following factors were considered

1 A change in the type of patients admitted for surgery During the study period a less favorable population was submitted for mitral valve replacement including older patients and a number with severe coronary disease Advanced age seemed to be a definite risk factor The median age for persons dying of TMD was 65 years Yet age was not the only explanation Two of the patients were in their early 50s and the underlying lesions were various As already noted anatomical studies suggested other indices of degeneration especially in the papillary muscles Left ventricular dysfunction however as ordinarily recognized did not appear to be a factor End diastolic pressures had usually been normal though some cases had low ejection fractions for their degree of mitral regurgitation

2 Characteristics of the Hancock valve As we first considered the etiology of TMD the Hancock valve itself naturally came under suspicion Temporally the relation was not altogether convincing While the porcine valve was used exclusively after June 1974 the first case of TMD was not recognized until November 1975 Yet the 2 cm downward projection of the rather angular Hancock struts makes it important to consider the area into which they will project and to size the valve before the heart is cardioplegic If the ventricle is small or the papillary muscle inserts close to the annulus one can visualize how damage might occur particularly if it became necessary to give external massage In three cases the fit of the prosthesis was snug There was however no consistent relation of strut to lesion the only predictable feature was proximity of lesion to papillary muscle In five of our cases the struts seemed much too remote and external massage had been used in only one case Furthermore ventriculographic studies have indicated to us that there is normally little basal movement of the papillary tips during ventricular contraction and the papillary tip is further separated from the mitral annulus after valve replacement Thus it seems unlikely that the papillary muscles were shaved off as the ventricle contracted against the struts In two cases (No 5 and 6) a strut was close enough to part of the tear to arouse suspicion We concluded that strut impingement was not the usual cause of TMD but that it might help initiate a tear particularly if the valve is misaligned or too large A distinctive characteristic of the Hancock valve is its flow pattern which produces a forceful central jet During ventriculography we have many times seen hosing of this jet often seeming to strike close to the anterior papillary muscle site Although this in itself seems to be an insufficient source for trauma it might be additive with other factors

3 Unrecognized operative trauma Though there was reason to suspect minor trauma in four cases the types were various and the resulting lesion was always grossly disproportionate In Case 5 (who had one of the deepest and most

extensive tears) a suction tip had been wedged in the papillary groove In the other cases no rigid apparatus was allowed in the ventricle and venting was done transmitrally with a Foley or soft plastic cannula Inadvertent nicking of the adjacent left ventricular wall may sometimes occur during removal of the mitral valve In each of our cases the leaflets were first detached above and then the papillary tips or chordae were cut using curved scissors One blade of these traveling in the area between the papillary tip and the adjacent left ventricular wall might accidentally open a natural transverse plane of cleavage In Cases 1 and 5 the clearance in this area seemed reduced Surgical trauma also appeared to be a possible factor in Case 3 where the lower arm of a complex tear developed adjacent to a closely cut papillary stump however it was difficult to accept this explanation for the rest of the very extensive lesion In four other patients the papillary tips were free standing and well separated from the ventricular wall Papillary and chordal resection except in Case 3 was conservative There was no instance of a button holed ventricle

4 Stretch damage and cardioplegia The coincidence between the introduction of cold and potassium induced cardioplegia[2] and the recognition of TMD appeared suggestive The techniques were gradually adopted during 1974 to 1976 and were used in seven of the eight cases The anatomy of the lesion suggested stretch damage Excessive traction on the mitral apparatus resulting in an abnormal lifting or bending of the papillary muscles seemed a good explanation for many of the pathological findings While the surgeons were not aware of exerting any unusual force they did note that during cardioplegia the heart appeared very easily deformable Perhaps this remarkable plasticity makes cardioplegic muscle more susceptible to inadvertent stretching Features of the lesion compatible with this were

1 Involvement of the papillary groove (Cases 4 and 6)

2 Discontinuous tears focused over the papillary sites (Cases 4 and 6)

3 Diffuse microscopic lesions of the ventricular wall perhaps explainable by inward tenting of a very pliant left ventricle attached to the lifted papillary muscle

4 Hemorrhages in the papillary root system Unfortunately there were difficulties with this theory as the complete explanation for TMD In four cases (No 1 2 5 and 7) the lesions were centered well above the papillary groove which probably would have been torn if papillary traction had been the chief cause There was also the strong implication that the lesion could result from some kind of cumulative stress In Case 4 where the anterior papillary muscle looked almost avulsed (Fig 5) rupture occurred 4¼ days after operation suddenly and agonally There was no necrosis and scarcely any fibrin on the exposed surfaces These observations implied an additional factor contributing to abnormal stretching of the ventricle

5 Stretch damage and the untethered left ventricle Would TMD have occurred with the same intraoperative trauma or stretching if the mitral valve had been left intact? We think not To the anatomist the mitral apparatus seems not a mere appendage of the left ventricle but an integral part of its structure The work of Armour and Randall[10] implies that papillary muscle chordae and leaflets form the inner arm of a longitudinally coursing loop connected at both ends with the mitral annulus The outer arm of this *mitral loop* is a large part of the thin superficial coat of the left ventricle which consists of longitudinal fibers fixed to the mitral annulus converging toward the apex and penetrating at various levels (as plunge fibers) through to the papillary muscles and trabeculae Together with the mitral apparatus these outer vertical fibers appear to form a binder for the thicker circumferential myocardial core and to provide an important source for longitudinal shortening of the left ventricle Thus detaching the papillary muscles from the annulus may be transsecting a major vertical fiber loop—and also removing a longitudinal binder One might guess that with each systole the outer long axis fibers (still attached to the mitral annulus) would tend to retract the fulcrum of the mitral loop—the base of the papillary muscle—into the left ventricular wall toward the apex increasing longitudinal stress on the remaining endocardium During diastole loss of the mitral rigging could also allow the untethered ventricle to overexpand longitudinally tending to pull apart its unbound transverse core (Fig 9) In four of our patients the left ventricular inflow tract had been strictured by chronic shortening of the mitral apparatus in three the mitral loop had probably been functionally destroyed but artifi

cially supported by long standing mitral prolapse[11] and in one it had been ischemic Perhaps such an area rendered cardioplegic unduly stretched and then suddenly untethered and forced to assume a new workload may acutely malfunction and dilate Such a process might be cumulative and would explain the phenomenon of delayed fiber separation and rupture without necrosis or a visible source of trauma This theory is also compatible with the other anatomical features of the lesion (1) its usual location just proximal to the papillary muscle without necessarily involving the papillary groove (2) its circumferential propagation (3) its development along natural lines of cleavage (4) the occurrence of parallel, complex, and discontinuous tears and (5) the microscopic evidence of diffuse changes sometimes seen at a distance from the obvious lesion Active retraction of the papillary muscle into the ventricular wall could explain pinching and rupture of blood vessels supplying its root system This retraction would also explain the divergence of the papillary muscle sites[11] which we not uncommonly see on angiograms after mitral valve replacement

The two sources of longitudinal stretch damage would obviously be additive The role of cardioplegia deserves further experimental study We need to know precisely what effects cold or potassium induced relaxation have on the tensile properties of the left ventricle and how long these last after cardioplegia is apparently reversed

Incomplete rupture and myocardial dysfunction

When TMD did not lead to immediate death it appeared to be profoundly destructive of myocardial *function* While there were sometimes contributing factors—i.e a small recent myocardial infarction in Case 7 and suturing of the left ventricle in Cases 5 and 8—pump failure in Cases 1 3 and 6 can scarcely be attributed to anything except TMD itself All these patients had fair or good left ventricles preoperatively The mechanism of dysfunction is not difficult to understand when the tear is very deep and extensive (as in Cases 3 and 5) but severe myocardial failure also occurred when the gross lesion was much less impressive The role of myocardial edema (Cases 3 and 6) and of more generalized microscopic disruption (Cases 1 2 and 7) may be important Cases 1 and 7 also suggest that some patients could survive TMD (without benefit of diagno[sis]) and that if it contributed to the cardiomy[opathy] sometimes seen after mitral valve replace[ment] the lesions viewed later would probably b[e] only myocardial thinning and endocardial fibros[is] with patchy involvement of circumferentia[l] fibers In fact these have been familiar autops[y] findings of cardiomyopathy associated wit[h] mitral replacement since the earliest experienc[e] with prosthetic valves[14] The course of Case [...] certainly also implies that cardiomyopathy ca[n] result from healed TMD

Repair and prevention

The present anatomic observations suggest [a] better method for surgical repair when complet[e] rupture occurs on the operating table Althoug[h] the external break appears to be small and longi[tudinal] the surgeon should recall that the inne[r] lesion is extensive and generally transvers[e] usually spiraling slightly upward from the anter[i]or to the posterior papillary area Repair of th[e] whole lesion requires placing sutures *deeply* an[d] securing *both* papillary sites Removal of th[e] valve and suturing from within may well b[e] preferable[4]

If the present concepts of etiology are correct i[t] would appear that valvular reconstruction a[s] done by Yacoub and DeGasperis[15] should elimi[nate] the problem When mitral replacement i[s] necessary several measures should be importan[t] in preventing TMD

1 During excision of the mitral valve carefu[l] avoidance of trauma to the area destined to b[e] stretched after the ventricle is untethered—par[ticularly] (a) surgical tension on the papillar[y] muscles in the cardioplegic heart and (b) wide[-]sized valves in small ventricles

2 Very careful and slow weaning of the cardioplegic heart from bypass to allow for return o[f] normal muscular tone before the myocardium i[s] subjected even to the stress of normal filling an[d] ejection At present we allow the rewarmed hear[t] to pump empty for 30 minutes and then adminis[ter] calcium chloride before even starting th[e] weaning process

3 The continued avoidance of ventricula[r] distention prophylactic use of unloading tech[ni]ques for several days in high risk patient[s] despite apparent hemodynamic well being With increasingly strict adherence to these principles

our operative mortality rate fell below 5% in 1977 In 1978 and in the first 6 months of 1979 there were no proven cases of TMD The diagnosis was suspected however in one non autopsied patient in whom the weaning protocol had not been used

In our original presentation[18] we also proposed that leaving the posterior leaflet intact during mitral valve replacement should reduce the risk of TMD Our surgeons have not used this approach, suspecting that it might provide a focus for embolism In 1964 however Lillehei and colleagues demonstrated that it was possible to insert a ball in cage prosthesis without removing the mitral valve Their goal interestingly was to reduce postoperative left ventricular failure Rastelli and co workers disputed this idea finding that in normal dogs studied 2 days after mitral valve replacement retention of valvular continuity made no difference to ventricular function These observations however may not apply to old sick mitral ventricles especially during the first minutes or hours after cold or potassium induced cardioplegia Furthermore anatomical studies by the same authors offer some evidence for the importance of preserving the mitral loop[19] Retaining even partial continuity between papillary muscle and annulus was found to prevent the otherwise inevitable infarction atrophy and retraction of the papillary muscles which followed mitral valve replacement The present study taken with a previous report on ventricular buckling in mitral prolapse[1] suggests that the mitral loop may be a factor in left ventricular function

Conclusions

Between late 1975 and 1977 transverse midventricular disruption (TMD) was our chief cause of death after mitral valve replacement The same lesion may produce acute power failure in the operating room or cardiac rupture the latter delayed sometimes as long as 4 days postoperatively The incidence of the problem apparently suddenly increased after the introduction of cold and potassium induced cardioplegia Many of the anatomic features suggest stretch damage The substrate of the lesion may be the untethered left ventricle produced by cross cutting the mitral loop But realization probably usually requires too rapid weaning of the cardioplegic heart from bypass and perhaps inadvertent stretch trauma to the very relaxed ventricle Surgical nicks or strut impingement of the Hancock valve seem less important factors Old mitrally damaged hearts appear the most susceptible TMD even when apparently mild appears to be associated with severe left ventricular dysfunction and sometimes diffuse microscopic disruption Long term follow up in one case suggests that the lesion may be a cause of the chronic cardiomyopathy sometimes seen after mitral valve replacement By changing our operative technique to include a 30 minute period of empty beating after reversal of cardioplegia we apparently have eliminated the fatalities No cases have been recognized in the last year When rupture does occur repair should take into account that the primary lesion is endocardial and above both papillary sites

REFERENCES

1 Treasure R L, Rainer W G Strevey T E, and Sadler T R. Intraoperative left ventricular rupture associated with mitral valve replacement Chest 66 511 1974
2 Gay W A Jr and Ebert P A Functional, metabolic and morphologic effects of potassium induced cardioplegia Surgery 74 284 1973
3 Gnepp R B Stinson, E B and Shumway N E Profound local hypothermia for myocardial protection during open heart surgery J Thorac Cardiovasc Surg. 66 731 1973
4 Sharratt G P Ross J K Monro J L, and Johnson A M. Intraoperative left ventricular perforation with false aneurysm formation Br Heart J 38 1154 19 6
5 Bjork V O Henze A and Rodriguez, L Left ventricular rupture as a complication of mitral valve replacement. Surgical experience with eight cases and a review of the literature J Thorac Cardiovasc Surg 73 14 19 7
6 Zacharias, A Groves, L K Cheanvechai, C Loop F D and Effler D B Rupture of the posterior wall of the left ventricle after mitral valve replacement J Thorac Cardiovasc Surg 69 59 19 5
7 MacVaugh H. III Joyner C R and Johnson, J Unusual complications during mitral valve replacement in the presence of calcification of the annulus Ann Thorac Surg 2 336, 19 1
8 Roberts W C and Perloff J K Mitral valvular disease A clinicopathologic survey of the conditions causing the mitral valve to function abnormally Ann. Intern Med 77 967 1972
9 Wareham E E and Bloomer W E in Bjork, V O., Henze A and Rodriguez, L Left ventricular rupture as a complication of mitral valve replacement Surgical experience with eight cases and a review of the literature J Thorac Cardiovasc Surg 73 21 19 7
10 Wolpowitz A Barnard M S Sanchez H E, and Barnard C N Intraoperative posterior left ventricular wall rupture associated with mitral valve replacement Ann Thorac Surg 25 551 1978.
11 Cobbs B W Jr and King S B., III Ventricular

buckling A factor in the abnormal ventriculogram and peculiar hemodynamics associated with mitral valve prolapse Am Heart J 93 741 1977
12. Cobbs B W Jr in Hurst J W ed The Heart New York 1974 McGraw Hill Book Company Inc pp 874 875 881 889
13 Armour J A and Randall W C Structural basis for cardiac function Am J Physiol 218 1517 1970
14 Roberts W C and Morrow A G Anatomic studies of heart containing caged ball prosthetic valves Johns Hopkins Med J 121 271 1967
15 Yacoub M H and DeGasperis C La Chirugia conservativa della mitrale G Ital Cardiol 8 (4)406 1978 (English abstract)
16 Cobbs B W Jr Hatcher C R Jr Craver J M., and Jones E L Transverse midventricular disruption after mitral valve replacement Circulation 56 (Suppl. 3) III 26 1977
17 Lillehei C W Levy M J and Bonnabeau R C Jr Mitral valve replacement with preservation of papillary muscles and chordae tendineae J Thorac Cardiovasc Surg 47 532 1964
18 Rastelli G C Tsakiris A G Frye R L and Kirklin J W Exercise tolerance and hemodynamic studies after replacement of canine mitral valve with and without preservation of chordae tendineae Circulation 35 (Suppl I) I 34 1967
19 Rastelli G C Kirklin J W and Titus J L Fate of papillary muscles after prosthetic replacement of mitral valve Mayo Clin Proc 42 210 1967

Experimental and laboratory reports

Autonomic tone of patients during an electrophysiological catheterization

The role of autonomic influences on the reproducibility of sinus node function studies

Gregory M Jewell M D *
Raymond D Magorien M D **
Stephen F Schaal M D ***
Carl V Leier M D ****
Columbus Ohio

In recent years invasive techniques have been used to obtain information about the electrophysiologic properties of the human heart These techniques of recording intracardiac electrograms and placement of intracardiac extrastimuli form the basis of the electrophysiological study which is oftentimes used to formulate therapy determine the need for pacemaker intervention etc It is reasonable to assume that the electrophysiological study which is performed in a setting of x ray units electronic equipment venesections cutaneous punctures and gowned personnel may induce a state of stress and apprehension in the patient According to the theory of Cannon and data from others the procedure should elicit a hyperadrenergic response with increased release of endogenous catecholamines As suggested by Strauss and colleagues[a] the hyperadrenergic response could modify the results obtained during the procedure specifically decrease the basic cycle length normalize the sinus node function studies and mask underlying sinus node dysfunction

This investigation was designed to determine whether the electrophysiological study induces a hyperadrenergic state to investigate the relationship between the adrenergic state and sinus node function results and to assess the reproducibility of the sinus node function studies

Methods and materials

Patient population Sixteen patients were studied The patients were divided into two groups on the basis of data derived from the sinus node function studies Group I consisted of eight patients (mean age 51 years six males two females) with normal sinoatrial conduction times (≤ 205 msec) and normal corrected sinoatrial recovery times (≤ 395 msec) Two of the patients had atherosclerotic coronary artery disease proven by catheterization The remaining patients did not have any clinically apparent heart disease The clinical indications for an electrophysiological study included pre syncope in five patients paroxysmal atrial tachycardia in two patients and paroxysmal atrial flutter in one patient Group II consisted of eight patients (mean age 60 years five males three females) with abnormal sinus node function studies (SACT > 205 msec and CRT > 395 msec or

From th Division of Cardiology Ohio State Un versity College of Medicine

Supported by a grant f om the S J Roessler Foundati n and by Grant No 7 31 from the Central Ohi Chapter of the Ameri an H art Associati n

Received for publication Aug 21 19 8

A epted for publication Nov 7 19 8

Reprint request Carl V Leier M D Division of Cardi logy Ohio State University Hospitals 6 3 M ans Hall 466 W T nth Av Columbus Ohio 43210

Division of Cardi logy Ohio Stat University College of Medicine

Instructor I Med cin D vis on of Card logy Ohio Stat Universi ty C lleg of Med cine

Associat Professor of Medi ne D vision of Card logy Ohio State Univ rsity Coll ge of M dicine

Ass stant Profess r of Med cin nd Pharmac logy D ision of Cardi logy Oh o State Univ rs ty College of Medicin Invest gator Central Ohi Chapter of the Am rican H art Associat on

000 8 03/80/010051 + 07$00 70/0

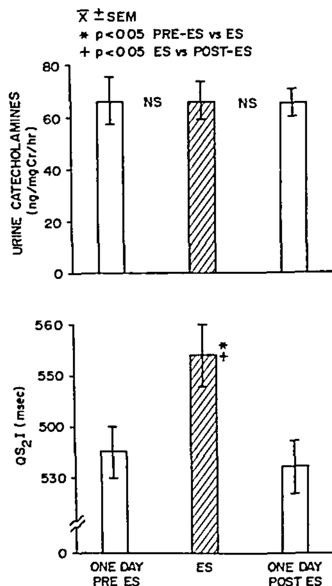


Fig 1 Urinary catecholamine excretion *(top panel)* and the QS_2I *(lower panel)* determined on the day before the electrophysiological procedure *(one day pre ES)* on the day of the electrophysiological procedure *(ES)* and one day after the procedure *(one day post ES)*

SACT > 205 msec alone) Two patients had catheterization proven atherosclerotic coronary artery disease and other than primary conduction abnormalities the remaining six patients did not have clinically apparent heart disease The clinical indications for an electrophysiological study in this group included sick sinus syndrome in four patients syncope in two atrioventricular block in one and paroxysmal atrial tachycardia in one

Procedure Written informed consent was obtained from each patient prior to study The adrenergic state of the patient was assessed by the determination of urinary catecholamine excretion[11] and by the measurement of the duration of electromechanical systole (QS_2I)[12] Urine was collected beginning 2 hours prior to the electrophysiological study and ending 2 hours after the completion of the study The mean duration of urine collection during the procedure day was 6 2 hours Six hour urine collections were also obtained during the same time of day one day prior to and one day after the electrophysiological study Patients remained supine during each urine collection period The three urine samples of each patient were analyzed by Bioscience Laboratories (Van Nuys California) for total catecholamine content (epinephrine and norepinephrine) and creatinine The total catecholamine content of each sample was corrected for creatinine excretion and was then divided by the time period of collection the results are expressed as nanograms of catecholamine excreted per milligram creatinine per hour Systolic time intervals were measured using previously described techniques[13] immediately prior to the sinus node function studies in the catheterization laboratory Systolic time intervals were also obtained 2 hours after the beginning of the 6 hour urine collection one day prior to and one day after the electrophysiological study The duration of total electromechanical systole (QS_2) was corrected for heart rate and expressed as total electromechanical systole index QS I

All medication was discontinued 48 hours prior to the electrophysiological study and no premedication was administered for the procedure The electrophysiological study was performed according to standard techniques All catheters were positioned with fluoroscopic assistance A bipolar catheter was placed in the high right atrium via a right antecubital vein venesection A bipolar recording catheter was passed into the esophagus to the level of the mid left atrium A six pole recording catheter was inserted into the right femoral vein (Seldinger technique) and was placed across the tricuspid valve[14] Intracardiac signals were amplified in a frequency range of 30 to 500 cycles/second and recordings were taken on an Electronics for Medicine DR 12 recorder at 50 and 100 mm /sec paper speed Atrial pacing and placement of atrial premature depolarizations (2× threshold) were accomplished by a Grass Instruments S88 stimulator and isolation

Table I Electrophysiological data obtained at the time of study (ES) and one day after the study (Post ES) in the subject population

Case No	Age/sex	SACT (msec)		CRT (msec)		EARP (msec)		AA (msec)	
		ES	Post ES	ES	Post ES	ES	Post ES	ES	Post FS
Normal SA node function group (Group I)									
1	47 M	187	189	193	182	220	310	783	843
2	58 M	179	169	300	180	290	200	840	822
3	56 M	183	182	175	245	310	280	937	774
4	29 F	130	134	29	136	220	210	605	730
5	58 M	163	161	243	193	300	330	773	895
6	64 M	164	127	207	125	250	230	819	857
7	35 F	135	124	85	165	230	250	440	831
8	63 M	50	140	109	119	220	240	1164	949
x̄	51	149	153	167	171	264	266	795	838
SD	13	45	25	68	47	38	43	214	68
SEM	5	16	9	31	15	13	15	76	24
Level of significance			NS		NS		NS		NS
Abnormal SA node function group (Group II)									
1	51 F	318	303	563	554	280	270	862	971
2	67 M	216	113	335	189	545	530	1192	1028
3	60 F	245	192	330	254	265	305	823	865
4	79 M	220	160	143	240	305	2 0	724	750
5	61 M	271	188	210	210	260	205	645	634
6	60 F	393	253	323	430	360	370	1376	753
7	47 M	2 2	356	509	457	450	420	1067	860
8	54 M	472	765	369	3 5	395	435	1143	928
x̄	60	295	279	348	332	358	351	973	849
SD	10	94	80	139	133	101	107	243	130
SEM	4	33	28	49	47	36	39	86	46
Level of significance			NS ($p < 0.1$)		NS		NS		NS

NS = not significant SACT CRT EARP and AA = see text

unit Systolic time intervals were performed within 15 minutes after the placement of the catheters Immediately after the completion of the systolic time intervals the sinus node function studies were started Sinus node function was assessed by the determination of the sinoatrial conduction time (SACT) and sinoatrial recovery time The SACT was obtained by the extrastimulus technique and equalled the A A interval minus the A A interval where A_1 = spontaneous atrial depolarization A = premature atrial depolarization (extrastimulus) and A_3 = the recovery atrial depolarization (sinus node origin) The SACT for each patient represents the mean of all determinations made at A A_2/A A_1 of 0 40 to 0 60 (sinus reset zone) Overdrive suppression with rapid atrial pacing was used to obtain the sinoatrial recovery time Atrial pacing at rates of 80 to 150 beats/minute (at 10 beats/minute increments) for greater than 30 seconds was used to suppress the sinus node The immediate post pacing recovery cycle was used for the sinoatrial recovery time The basic cycle length (AA interval) was subtracted from the sinoatrial recovery time and the difference was then expressed as the corrected recovery time (CRT) Each CRT value for each patient represents the mean of all the CRTs obtained during the sequence of atrial pacing a minimum of six values was used Normal values for our laboratory are SACT ≤ 205 msec and CRT ≤ 395 msec

After the electrophysiological study the esophageal and six pole catheters were removed The patient was returned to his hospital room with the high right atrial catheter sutured in place The position of this right atrial catheter was not changed from the beginning to the end of the study period At the same time one day following

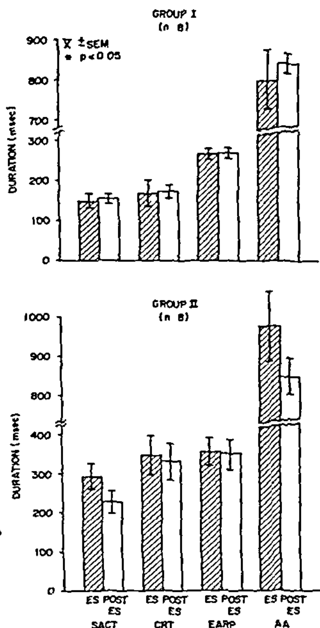


Fig 2 Electrophysiological data obtained on the day of the procedure *(ES)* and one day later *(post ES)* in patients with normal (Group I *top panel*) and in patients with abnormal (Group II *lower panel*) sinus node function studies *AA CRT EARP* and *SACT* = see text

the electrophysiological study, repeat sinus node function studies were performed in the patient s room The SACT and CRT values were obtained immediately after the systolic time intervals and approximately two hours after the beginning of the six hour urine collection for that day

The t test for paired data was used to analyze the statistical significance of changes between results obtained during the electrophysiological study and that obtained one day after the study

Results

The adrenergic state of the patients as measured by urinary catecholamines and the QS_2I during one day prior to and one day after the electrophysiological study are presented in Fig 1 The mean urine catecholamine excretion was not significantly different during the catheterization procedure than during comparable time periods the day before and the day after the procedure The mean QS_2I obtained during the electrophysiological study was significantly longer than the mean QS_2I values obtained (in the patient s room) one day prior to and one day following the procedure

The electrophysiological data are presented in Table I and are illustrated in Fig 2 The mean basic cycle length (AA interval) obtained in the hospital room on the day following the electrophysiological study did not differ significantly from that noted during the procedure

The mean SACT of the normal SA node function group (Group I) did not change significantly from the procedure day to the day following the study (Fig 3*A*) Although the SACT of patient No 8 (Group I) increased by 90 msec none of the patients in Group I demonstrated an increase of the SACT to the abnormal range the day following the procedure The mean SACT of the patients with abnormal sinus node function (Group II) decreased slightly the day following the electrophysiological study Although this change was not statistically significant it is noteworthy that the SACT decreased in all patients of this group except in patient No 7 If patient No 7 is excluded the mean SACT of Group II decreased significantly the day following the electrophysiological study Patients No 2 6 and 8 decreased their SACT > 100 msec and patients No 2 through 5 normalized their SACT the day following the procedure

The mean CRT did not change significantly for either group (Fig 3*B*) None of the patients with normal SA node function (Group I) prolonged CRT to the abnormal range on repeat study One of the Group II patients with initial normal CRTs prolonged the CRT to the abnormal range the day after the procedure The two patients with abnormally prolonged CRTs remained in the abnormal range on re study

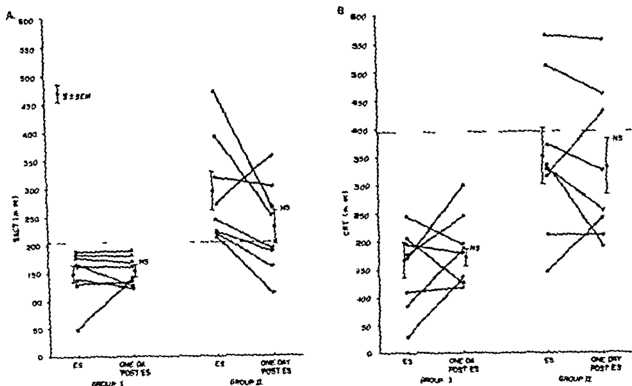


Fig 3 The SACT (*panel A*) and CRT (*panel B*) values obtained during the electrophysiological procedure (*ES*) and one day later (*one day post ES*) of individual patients with normal (Group I) and abnormal (Group II) SA node function studies While the mean SACT of Group II did not change significantly considerable variation in the SACT of individual patients over the two consecutive days was noted (*panel A right graph*) While the CRT decreased in five patients of Group II none of the values normalized on repeat study (*panel B right graph*) One Group II patient prolonged his CRT into the abnormal range NS = not significant

The mean atrial effective refractory period of either group was not significantly different on the day following the electrophysiological study when compared to values obtained from the procedure The mean atrial refractory period of Group II was significantly longer than that of Group I (t test for unpaired data) this may be secondary to the longer (but insignificant) basic cycle length of Group II

Discussion

The increase in the QS_2I coupled with a lack of change in the urinary catecholamine excretion during the electrophysiological study suggest that the procedure did not elicit a hyperadrenergic response The electrophysiological study performed in the catheterization laboratory appears more basal than the shorter and less involved procedure performed in the patient s hospital room These results are at variance with the general impression that the electrophysiology laboratory is a continuously stressful situation for the patient and with the results of Edmondson and associates and Turton and colleagues[3] showing that procedures specifically dental work and cardiac catheterization respectively increase plasma catecholamines However the plasma samples of these two studies were drawn at a time when the procedures were quite stressful and therefore may not be representative of the adrenergic state of the entire procedure The short half life of circulating epinephrine and norepinephrine and the body s ability to increase these substances rapidly make the plasma catecholamine concentration merely a value reflecting the adrenergic state of a patient over a very short time period [ ] The urine catecholamines provide a physiological integration of plasma catecholamine concentrations over the period of time the urine sample is collected [ ] It is possible that the plasma catecholamine levels were high early in the electrophysiological study (during instillation of local anesthesia venesection etc) and returned toward the basal state as the

patient became acclimated to the environment of dim lights and classical music It is somewhat surprising that the QS_2I was shorter in the hospital room than in the electrophysiology laboratory this may be a reflection of the hospital activities of the day including venepunctures physician rounds and discussions

The electrophysiological results of the patients with normal sinus node function (Group I) appears to be quite reproducible despite a probable mild increase in the adrenergic tone (decrease of the QS_2I) on the day following the complete electrophysiological study The mean basic cycle length (AA interval) of Group I patients was slightly shorter during the electrophysiological study primarily as a result of patient No 7 who had sinus tachycardia during the procedure If the results from patient No 7 are deleted the mean cycle length of Group I showed a tendency to decrease on the day following the procedure this is similar to the basic cycle length changes of Group II and supports the hypothesis that the over all adrenergic tone for both groups was slightly greater the day following the procedure A concomitant increase in the parasympathetic tone during the procedure cannot be definitely excluded The SACT and CRT are both corrected for the spontaneous cycle length so that mild changes in the adrenergic tone would not be expected to result in a significant change in the corrected values In general, it appears that when sinus node function studies obtained from the standard electrophysiological study are normal (Group I patients) the results are reproducible

While the mean measurements of sinoatrial function in patients with sinus node dysfunction (Group II) did not change significantly considerable variation in individual results occurred between the two consecutive study days The basic cycle length decreased in five the SACT shortened in seven and the CRT decreased in five of the eight patients on the day following the electrophysiological study Four patients normalized their SACT values the day after the procedure Urine catecholamine and QS I data do not show that these patients had greater adrenergic tone than the control group during the day following the procedure It appears that in some patients the electrophysiological study induces an absolute or relative (reduced adrenergic tone) increase of parasympathetic tone this would tend to lengthen the basic cycle length and prolong the SACT and CRT Somnolence the quiet and dimly lit room placement and manipulation of catheters in veins (vasovagal) and a catheter in the esophagus (vagovagal) might have increased the parasympathetic tone of some of the patients undergoing the complete electrophysiological study However since very few of the patients in the control group were noted to have a longer SACT, CRT or cycle length during the standard electrophysiological study (compared to the day after the procedure) the sinoatrial region of some patients with abnormal SA node studies appears to respond more dramatically to an increase of parasympathetic tone Using the general classification advanced by Jordan and colleagues [6] and by Thormann and associates the four patients of Group II that normalized their sinoatrial studies specifically the SACT (patients No 2 through 5 Table I Fig 3) probably belong to the disturbances in autonomic regulation of sinus node function group and the remaining patients in Group II have intrinsic sinus node disease

It is unlikely that the parasympathetic effects on the sinoatrial function studies of some patients in Group II are secondary to a sympathetic induced parasympathetic tone mechanism [3] Similar responses were not noted in the control group and the urine catecholamines were not elevated

It is apparent that the electrophysiological study performed in a catheterization laboratory does not elicit a continuous hyperadrenergic response in most patients undergoing the procedure in fact the event appears to induce an absolute or relative increase in parasympathetic tone in some patients Current measurements of sinoatrial function (SACT and CRT) as performed in the electrophysiology laboratory are reproducible in patients with normal baseline SA node function In patients with abnormal SA node function studies additional pharmacologic and/or physiologic maneuvers [1,2] should be performed in order to differentiate patients into those with intrinsic sinus node disease and those with abnormal autonomic regulation

Summary

Urinary catecholamine excretion remained unchanged and total electromechanical systole QS I increased during the electrophysiological study of 16 patients (eight normals eight with

ius node dysfunction) when compared to values tained the day before and the day after the idy The mean values of the sinus node func on studies (sinoatrial conduction and recovery nes) repeated the day after the procedure were t significantly different from those obtained iring the electrophysiological study in both the ormal patients and patients with sinus node sfunction Individual patients in the sinus node sfunction group showed slight variation in the nus node studies four of these patients showed ormalization of SA node function the day after ie electrophysiological procedure

These studies suggest that the electrophysio gical procedure does not provoke a hyperadre ergic state The sinus node function studies are eproducible in patients with normal baseline alues While the mean sinus node function esults for the group with abnormal SA node inction did not change significantly on repeat esting some individual variation occurred this ariation is probably related to autonomic distur ances of SA node function

The authors wish to thank Ms Max Bacher and Ms Barbara Metzner for their assistance in the preparation of this manuscript

REFERENCES

1 Cannon W Bodily Changes in Pain Hunger Fear and Rage New York 1915 D Appleton & Co
2 James T N Bear E S, Lang K R Gree E W, and Winkler H H Adrenergic mechanisms in the sinus node Arch Intern Med 125 51? 1970
3 Carlson L A Levi L and Oro L Plasma lipid and urinary excretion of catecholamines in man during experimentally induced emotional stress and their modification by nicotinic acid J Clin Invest 47 1795 1968
4 Taggart P Parkinson P and Carruthers M Cardiac responses to thermal physical and emotional stress Br Med J 3 71 1972
5 Turton M B Deegan T and Coulshed N Plasma catecholamine levels and cardiac rhythm before and after cardiac catheterization Br Heart J 39 130, 1977
6 Edmondson H D Roscoe B and Vickers M D Biochemical evidence of anxiety in dental patients Br Med J 4 7 1972
7 Kopin I J Catecholamines, adrenal hormones, and stress Hosp Pract 11 49 1976
8 Strauss H C Gilbert M, Svenson R H, Miller H C and Wallace A G Electrophysiologic effects of propranolol on sinus node function in patients with sinus node dysfunction Circulation 54 452 1976
9 Engel T R Bond R C, and Schaal S F First degree sinoatrial heart block sinoatrial block in the sick sinus syndrome Am Heart J 91 303 1976
10 Engel T R and Schaal, S F Digitalis in the sick sinus syndrome Circulation 48 1201 1973
11 von Euler U S Quantitation of stress by catecholamine analysis, Clin Pharmacol Ther 5 398 1964
12 Lewis R P Boudoulas H Forester W F, and Weissler A M Shortening of electromechanical systole as a manifestation of excessive adrenergic stimulation in acute myocardial infarction Circulation 46 856 1972
13 Lewis R P Leighton R F Forester W F and Weissler A M Systolic time intervals, *in* Noninvasive Cardiology Weissler A M ed New York 1974 Grune & Stratton Inc p 301
14 Scherlag B J Lau S H Helfant R H, Berkowitz W D Stein E and Damato A N Catheter technique for recording His bundle activity in man Circulation 39 13 1969
15 Strauss H C, Saroff A L Bigger J T and Giardina E G V Premature atrial stimulation as a key to the understanding of sinoatrial conduction in man Circulation 47 86 1973
16 Narula O S Samet P and Javier R P Significance of the sinus node recovery time Circulation 45 140 1972
17 Mandel W J Hayakawa H, Allen H N Danzig R and Kermaier A I Assessment of sinus node function in patients with sick sinus syndrome Circulation 46 761 1972
18 Wurtman R J Catecholamines N Engl J Med 273 637 693 1965
19 Axelrod J and Weinshilboum R Catecholamines, N Engl J Med 287 237 1972
20 Jordan J L Yamaguchi I and Mandel W J Studies on the mechanism of sinus node dysfunction in the sick sinus syndrome Circulation 57 217 1978
21 Thormann J Schwarz F Ensslen R and Sesto M Vagal tone significance of electrophysiological findings and clinical course in symptomatic sinus node dysfunction Am Heart J 95 725 1978
22 Schlesinger Z Barzilay J Stryjer D and Almog C H Life threatening vagal reaction to emotional stimuli Isr J Med Sci 13 59 1977
23 Taggart P Hedworth Whitty R Carruthers M and Gordon P D Observations on electrocardiogram and plasma catecholamines during dental procedures the forgotten vagus Br Med J 2 787 1976
24 Dighton D H Sinus bradycardia autonomic influences and clinical assessment Br Heart J 36 791 1974

Antihypertensive effect of BS 100-141,* a new central acting antihypertensive agent

Somchart Lochaya M D F A C C F R C P (C)
Vipa Thongmitr M D
Orawan Suvachittanont M D
Bangkok Thailand

N Amidino 2 (2 6 dichlorophenyl) acetamide hydrochloride (BS 100 141) is a phenylacetyl guanidine derivative which exerts an antihypertensive effect by stimulating central alpha adrenoreceptors[1,2] This causes a reduction of sympathetic activity and depresses pressor circulatory reflexes[2] At the same time it stimulates peripheral alpha adrenoreceptors and therefore orthostatic hypotension is prevented[1] The mechanism of its hypotensive effect is therefore similar to clonidine the sedative effect is however reported to be less The purpose of the present trial was to determine the antihypertensive effect and dosage level in a population of Thai outpatients

Methods

Thirty six patients of both sexes were studied as outpatients at the University Hospital Each patient in the study had been followed previously in the hypertensive clinic for several months or years and therefore knew the investigators and was familiar with the environment of the clinic Written informed consent was obtained from each patient Inclusion into the study required that the subject s age was 65 years or less and that his average diastolic blood pressure was 95 mm Hg or higher after at least one week of placebo Only cooperative patients without malignant hypertension or other serious and incapacitating illnesses were studied All had a complete history and physical examination Laboratory tests included hemoglobin hematocrit white cell count sedimentation rate urinalysis chest x ray electrocardiogram B U N creatinine uric acid sodium potassium chloride alkaline phosphatase glutamic oxaloacetic transaminase, glutamic pyruvic transaminase and fasting blood sugar In addition rapid intravenous pyelograms and appropriate tests for pheochromocytoma were performed when indicated

Following at least one week of placebo the patients accepted into the study were assigned at random to two groups Nineteen patients received BS 100 141 and seventeen received BS 100 141 placebo The placebo tablets were indistinguishable from active tablets Each tablet of BS 100-141 contained 2 mg of the drug All medications were given orally The initial dose was 4 mg of BS 100 141 per day or two tablets of placebo given in two divided doses The patients were seen at intervals of one week for the next seven weeks On subsequent visits at the interval of one week the physician added one tablet (2 mg) of BS 100 141 or placebo if the standing diastolic blood pressure was more than 90 mm Hg An increment of 4 mg was given if the patient had already been taking 8 mg of BS 100 141 during the previous week The maximum dose was 12 mg per day or two tablets of placebo three times a day If the standing diastolic blood pressure was less than 90 mm Hg the dose was maintained Non responders were removed from the study if the blood pressure did not fall following a week of 12 mg of BS 100 141 or six tablets of placebo Blood pressure and heart rate were taken in the supine and standing position both immediately and 3 minutes after assuming this posture, and in the sitting position The

From the Division of Cardiology Department of Medicine Ramathibodi Hospital, Faculty of Medicine Mahidol University Bangkok, Thailand

Received for publication Sept 6 1978

Accepted for publication Oct 10 1978

Reprint requests Dr Somchart Lochaya, Division of Cardiology Department of Medicine Ramathibodi Hospital, Faculty of Medicine Mahidol University Bangkok, Thailand

*Guanfacine (Estulic) Sandoz Pharmaceuticals

0002-8703/80/010058 + 06$00 60/0 © 1980 The C V Mosby Co

measurement was made with a standard sphygmomanometer following at least 15 minutes of rest Cessation of sound was our criterion for diastolic blood pressure All patients were told to omit the morning dose before coming for the examination The patients were questioned concerning symptoms and were examined for adverse effects If side effects interfered with the daily routine of the patient the drug dosage was reduced to the level of the previous visit and either 50 mg of hydrochlorothiazide or 2 5 mg of bendroflumethiazide were added The body weight was recorded at each visit Laboratory tests were repeated at the end of the study

Results

Patient characteristics All patients were of Thai or Thai Chinese origin There were 11 men and eight women in the BS 100 141 group as against seven men and 10 women in the placebo group They all suffered from mild hypertension [3] The body weight of the BS 100-141 group was significantly higher (Table I) but sex age duration of hypertension and family history of hypertension were not statistically different *Analysis of the data at the end of the initial* placebo period indicated that there were no significant differences in regard to supine standing and sitting blood pressure or pulse rate in supine and sitting The standing pulse rate of the placebo group was higher compared to the BS 100-141 group All patients in the BS 100-141 group completed the study whereas 12 patients in the placebo group were removed from the study as non responders The number of patients and the daily dosage at the end of the treatment period are shown in Table II 7 patients in the BS 100 141 group and one patient under placebo received a diuretic

Antihypertensive effects of BS 100 141 The effect of BS 100-141 and placebo on blood pressure and heart rate was compared statistically within the treatment groups by means of the Wilcoxon Rank Sum Test (level of significance 2 alpha = 0 05) The values of visit 2 (after treatment with placebo for 1 week) were compared with the values at visits 3 to 9

As can be seen from Table III there was a significant decrease of the blood pressure under BS 100 141 from visits 3 to 9 in all postures With placebo the comparison could only be made until visit 7 by visits 8 and 9 there was too much missing date because of dropouts for ineffectiveness With few exceptions no significant change in blood pressure was observed under placebo The heart rate (Table IV) decreased significantly in the actively treated group in the supine and sitting postures whereas in the standing posture the differences were not statistically significant In the group under placebo treatment no statistical evaluation was indicated since pulse rate did not change

The comparison between the two groups elicited the following data The homogeneity of the two groups regarding the baseline blood pressure and heart rate was tested by means of the U test With the exception of the heart rate in the standing posture no differences were observed between the two groups

The differences between the values obtained at visits 3 to 7 and the baseline value (visit 2) in the BS 100 141 group have been compared with the corresponding differences in the placebo group using the U test according to Mann Witney and Wilcoxon The values of visits 8 and 9 of the placebo group could not be evaluated for reasons already mentioned This comparison showed

Table I Age weight duration of illness

	Age (years)		*Weight (kg)*		*Duration (years)*	
	BS 100 141	*Placebo*	*BS 100 141*	*Placebo*	*BS 100-141*	*Placebo*
Mean	51	48	67	59	6 7	5 9
Standard deviation	7	10	11	11	5,7	5 5
Median	49	45	69	58	4,5	5 0
Range	39-60	35-65	51 86	45-83	1 20	0-19
n	19	17	19	17	18	15

Table II Dosage of BS 100 141 and placebo Number of patients with number of tablets daily at the end of the treatment period in each group

	BS 100 141	*Placebo*
1 tablet daily	1 patient	0 patients
2 tablets daily	8 patients	0 patients
3 tablets daily	2 patients	1 patient
4 tablets daily	4 patients	0 patients
6 tablets daily	4 patients	16 patients

Table III Blood pressure (mean values ± standard deviation)

Visit	*Supine*				*Sitting*				*Standing*			
	Syst.	*Diast*	*Syst*	*Diast*	*Syst*	*Diast*	*Syst*	*Diast*	*Syst*	*Diast*	*Syst*	*Diast*
1	154 ± 17	9[illegible] ± 8	1[illegible]0 ± 2[illegible]	101 ± 10	147 ± 19	104 ± 17	143 ± 26	10[illegible] ± 27	150 ± 20	105 ± 11	148 ± 27	102 ± 14
	Placebo				Placebo				Placebo			
2	160 ± 18	102 ± 7	160 ± 19	10[illegible] ± 7	1[illegible]9 ± 20	10[illegible] ± 7	1[illegible]4 ± 20	10[illegible] ± 8	159 ± 17	110 ± 7	161 ± 22	111 ± 10
	Placebo		BS 100-141		Placebo		BS 100-141		Placebo		BS 100-141	
3	158 ± 15 n.s	100 ± 7 n.[illegible]	145 ± 15	97 ± 10	1[illegible]0 ± 15 n.s.	99 ± 7	130 ± 20	91 ± 12	153 ± 16 n.s.	106 ± 10	131 ± 20	94 ± 14
4	1[illegible]4 ± 19 n.s.	9[illegible] ± 8	14[illegible] ± 20	97 ± 11	1[illegible]0 ± 27 n.s.	100 ± 10	133 ± 21	9[illegible] ± 11	153 ± 21 n.s.	104 ± 9	132 ± 22	9[illegible] ± 11
5	161 ± [illegible]0 n.s	103 ± 9 n.s.	143 ± 20	92 ± 10	1[illegible]8 ± 18 n.s	106 ± 28 n.s.	130 ± 21	91 ± 11	160 ± 21 n.s.	107 ± 11 n.s.	134 ± 22	98 ± 13
6	168 ± 2[illegible] n.s.	104 ± 8 n.s.	1[illegible]0 ± 20	97 ± 9	160 ± 17 n.s.	111 ± 18 n.s	133 ± 15	93 ± 9	161 ± 21 n.s	108 ± 10 n.s.	133 ± 19	9[illegible] ± 11
[illegible]	163 ± 15 n.s.	104 ± [illegible] n.s	142 ± 19	93 ± 10	160 ± 19 n.s	104 ± 10 n.s	128 ± 20	88 ± 9	159 ± 19 n.s	108 ± 12 n.s	128 ± 19	90 ± 10
8	168 ± 10	103 ± 5	146 ± 27	93 ± 13	164 ± 16	99 ± 10	130 ± 26	90 ± 14	16[illegible] ± 10	108 ± 8	129 ± 23	92 ± 10
9	158 ± 21	104 ± 5	142 ± 19	94 ± 9	160 ± 14	106 ± 7	129 ± 16	8[illegible] ± 10	152 ± 14	112 ± 10	129 ± 15	96 ± 8

$p < 0.0$[illegible]
$p < 0.01$
$p < 0.001$

Table IV Heart rate (mean values ± standard deviation)

Visit	*Supine*		*Sitting*		*Standing*	
1	69 ± [illegible]	[illegible] ± 8	[illegible]3 ± 10	[illegible]4 ± 10	77 ± 9	[illegible]6 ± 8
	Placebo		Placebo		Placebo	
2	[illegible]3 ± 8	[illegible]1 ± 9	[illegible]6 ± 8	[illegible]3 ± 9	82 ± 7	77 ± 8
	Placebo	BS 100 141	Placebo	BS 100-141	Placebo	BS 100-141
3	[illegible]3 ± [illegible] —	6[illegible] ± 8	[illegible]7 ± 7 —	[illegible]0 ± 8	78 ± 5 —	[illegible]3 ± 10 n.s.
4	[illegible] ± [illegible] —	63 ± 9	[illegible]5 ± 8 —	6[illegible] ± 10	80 ± 7 —	72 ± 10 n.s
[illegible]	[illegible]3 ± [illegible] —	6[illegible] ± 11 n.s.	[illegible]7 ± 9 —	68 ± 11	77 ± 7 —	75 ± 11 n.s.
6	[illegible]2 ± [illegible] —	[illegible]1 ± 8	[illegible] ± 7 —	69 ± 12	80 ± 10 —	71 ± 10 n.s
[illegible]	[illegible]4 [illegible] —	6[illegible] ± 9	77 ± 9 —	68 ± 9 n.s	83 ± 11 —	72 ± 10 n.s.
8	[illegible]8 ± [illegible] —	[illegible] ± 9	[illegible]6 ± 5 —	69 ± 11 n.s.	82 ± 8 —	74 ± 11 n.s.
[illegible]	83 ± 10 —	[illegible] ± 8 —	82 ± 12 —	6[illegible] ± [illegible] —	68 ± 7 —	69 ± 13 —

$p < 0.05$

Table V Number and kind of side effects in each treatment group

	BS 100 141	Placebo
Dry mouth	17 patients	2 patients
Insomnia	7 patients	1 patient
Fatigue	6 patients	1 patient
Dizziness	4 patients	1 patient
Palpitations	2 patients	1 patient
Anxiety	2 patients	0 patients
Anorexia	1 patient	0 patients
Orthostat hypotension	1 patient	0 patients
Constipation	1 patient	0 patients
Headache	0 patients	1 patient
Total side effects/Number of patients	41/15	7/3

significant differences between the average blood pressure values in all postures and in heart rate in the sitting and supine postures in favor of BS 100-141

Dosage of BS 100 141

The dosage of BS 100-141 At the end of the study can be seen in Table II Fifteen patients received 2 to 8 mg /day eight of whom were on 2 mg twice a day In the four patients in whom the dosage was increased from 8 to 12 mg /day for the last 2 or 3 treatment weeks no additional benefit was obtained

Side effects (Table V) The most important side effects related to BS 100 141 were dry mouth insomnia fatigue and dizziness In general these side effects were of mild nature and did not interfere with the everyday activity of the patients A transitory reduction of the dosage had to be performed six times because of dry mouth fatigue dizziness or insomnia In no patient did the treatment have to be interrupted because of side effects Neither orthostatic hypotension nor edema were observed in this group of patients

Estimation of drug effectiveness

A scoring of drug efficacy was made at each visit by comparing the reduction of blood pressure to that obtained in the previous visit Table VI summarizes the results following one week of 4 mg /day of BS 100 141

The result demonstrates a favorable effect of BS 100 141 with 14 patients in the excellent and good groups is compared with two cases in the placebo group

Table VI Physician s estimation of efficacy

Efficacy after 1 week of treatment	BS 100-141	Placebo
Excellent	10 patients	1 patient
Good	4 patients	1 patient
Fair	1 patient	1 patient
Slight	1 patient	3 patients
None	3 patients	10 patients
Worse	0 patients	1 patient
Binomial probability	2 p < 0 001	n s

(Excellent + good + fair vs slight + worse), χ^2—statistic (between groups) χ^2 = 14 51—2p < 0 001

Excellent = reduction of standing diastolic blood pressure of 90 mm Hg or below Good = reduction of 50% or more of standing blood pressure that is above 90 mm Hg Fair = reduction of less than 50% of standing blood pressure that is above 90 mm Hg Slight = minimal reduction of blood pressure

Laboratory investigations

Serum potassium sodium chloride uric acid blood glucose blood urea nitrogen SGOT and SGPT and alkaline phosphatase obtained during control and at the end of the treatment remained unchanged Blood glucose and uric acid increased significantly during BS 100-141 treatment Hyperuricemia occurred in all seven patients on BS 100 141 to whom a diuretic had been given Fasting blood sugar increased in all patients except three Two patients were known to be diabetic a diuretic was added in seven patients The level of glucose did not rise above the upper limits of normal except in two patients one of whom was a diabetic Sedative effects did not occur

Hypertensive rebound

Following the completion of the study the treatment with BS 100 141 was discontinued and various antihypertensive agents were substituted which had previously proved effective in the individual patients The patients were given an appointment for a follow up visit within two weeks

With clonidine it is known that the occurrence of so called rebound hypertension is frequent This term is not exactly characterized but in general it is assumed that rebound hypertension is present if the blood pressure rises considerably above the values measured before active treatment (diastolic 130 mm Hg or more) and if at the same time distinct signs of sympathetic over

Table VII

Case no	Age	Sex	Final dosage of BS 100 141 mg /day	Drug taken after BS 100 141	Blood pressure before BS 100 141 treatment		Blood pressure under BS 100 141	Blood pressure 2-4 days after interruption
1	61	male	8	Hydrochlorothiazide	Supine	170/110	150/100	180/124
					Standing	180/110	140/100	156/120
					Sitting	150/104	138/90	154/132
6	49	male	6	Iso Triraupin	Supine	170/120	140/100	166/124
					Standing	180/130	140/108	122/126
					Sitting	170/130	140/102	–
14	49	male	6	Prazosin	Supine	140/110	112/94	114/110
			+ Pluryl K	Pluryl K	Standing	140/110	114/96	160/132
					Sitting	124/100	116/90	166/120
16	61	female	8	Iso Triraupin	Supine	160/100	122/78	170/120
					Standing	160/100	130/84	–
					Sitting	160/100	124/76	170/124

charge are observed–mainly tachycardia abdominal cramps pilar erection anxiety etc

Four patients in our series showed a rise in blood pressure in the days following discontinuation of the treatment (see Table VII) The symptomatology is described below Whether a classical rebound phenomenon occurred in these cases or whether there was merely a reappearance of the previously existing hypertension is open to discussion The cases were Nos 1 6 14 and 16

Case No 1 A 61 year old grocer had been treated for his hypertension for one year Control lood pressure following one week of placebo was 70/110 182/114 and 158/104 under BS 100 141 it decreased to 150/100 140/100 and 138/90 mm Hg in the supine standing and sitting posture respectively The dosage of BS 100 141 was 8 mg daily Except for dry mouth and dizziness of mild degree during the drug trial his course was uneventful After the trial 50 mg hydrochlorothiazide per day was substituted for BS 100 141 Two days following cessation of BS 100 141 severe headache developed requiring an analgesic He became unwell and had palpitations The symptoms lasted to the time of examination ten days later His blood pressure then was 180/124 156/120 154/132 mm Hg in the supine standing and sitting posture respectively Alphamethyl dopa was added and the patient was normotensive when reexamined a week later

Case No 6 A 49 year old colonel was a known hypertensive for 10 years He had not been taking any antihypertensive drugs for the previous two months before entering the BS 100 141 drug trial His blood pressure following a week of placebo was 170/120 182/134 and 170/132 mm Hg in the supine standing, and in the sitting posture respectively After taking BS 100 141 6 mg daily the blood pressure was 140/100 140/108 and 140/102 mm Hg respectively The only svmptom during the drug trial was insomnia which occurred during the last four weeks At the end of the trial 1 tablet of Iso Triraupin twice daily was substituted for BS 100 141 The patient developed headache palpitations restlessness and insomnia two days following cessation of BS 100 141 His blood pressure was elevated to 166/124 and 172/126 mm Hg in the supine and standing positions

Case No 14 A 49 year old male school teacher was a known hypertensive for over 20 years He complained of fatigue while taking 8 mg BS 100 141 so the dose was reduced to 6 mg and 1 tablet of Pluryl K was added His blood pressure decreased from a control level of 140/110 140/110 and 130/110 mm Hg to 112/94 114/94 and 116/90 mm Hg in the supine standing and sitting positions respectively At the end of the treatment prazosin 4 mg and 50 mg of hydrochlorothiazide daily were substituted for BS 100 141 He was seen four days later with palpitations and chest discomfort Blood pressure was elevated to 154/110 160/132 and 166/120 mm Hg in the supine standing and sitting positions respectively The medications were changed to propranolol 80 mg alphamethyl dopa 750 mg and hydrochlorothiazide 50 mg Blood pressure was normal at the following examination a week later

Case No 16 A 61 year old housewife was

known to be hypertensive for the past 2 years She was asymptomatic taking 8 mg of BS 100 141 and her control blood pressure which had been 160/102 162/104 and 150/100 mm Hg in the supine standing and sitting position became normal Iso Triraupin* was given following the cessation of BS 100 141 She was seen 3 days later when she complained of fatigue and giddiness Her blood pressure had risen up to 170/120 mm Hg in the supine and 170/124 mm Hg in the sitting position

Discussion

BS 100 141 a new antihypertensive guanidine derivative has been compared with placebo in a double blind trial in 36 patients (19 active 17 placebo) The average blood pressure of the patients under active treatment was significantly lowered from the first week of the trial onwards whereas the patients under placebo showed prac tically no effect In 14 of the 19 patients under treatment with BS 100 141 the diastolic blood pressure fell to 90 mm Hg or less already in the first week The dose range of BS 100 141 was between 4 and 8 mg daily An increase of the dosage from 8 to 12 mg per day which was tried in four patients did not improve the therapeutic results Orthostatic hypotension was not ob served this may be due to the peripheral alpha stimulating effect of the drug[1] Although there was a significant reduction of the pulse rate in the sitting position it was never 60 per minute in either position Our findings are in agreement with those of other investigators

BS 100 141 was generally well tolerated and no serious side effect was recorded during the entire period of treatment There were secondary side effects however and in one case the dose had to be reduced but the treatment was never inter rupted because of untoward reactions The most frequently occurring side effects were

dry mouth	17 patients
insomnia	7 patients
fatigue	6 patients
dizziness	4 patients

Three patients under placebo reported seven side effects of the same nature

The only biochemical change of potential importance was a tendency to an increase in blood glucose Close observation of the blood sugar is therefore indicated in patients with preexisting diabetes mellitus

After a sudden interruption of the treatment in four of 19 patients the blood pressures rose to pretreatment values or slightly higher without any serious consequences Discontinuation of the treatment however should be done gradually

Iso-Triraupin is manufactured by Boehringer GmBH Mannheim W Germa y

Summary

A double blind comparison between BS 100 141 and placebo in 36 hypertensive patients of Thai or Thai—Chinese origin revealed that the prepara tion lowers the elevated blood pressure within the first week of treatment in most patients The drug was relatively well tolerated and caused mild side effects only After a sudden discontinuation of the drug the blood pressure in four of the 19 patients increased within a few days to pretreatment values or slightly above The occurrence of rebound hypertension cannot be excluded Inter ruption of treatment therefore should be made gradually

We gratefully acknowledge the help of Sinporn Thaitar wayanon for her assistance and thank Sandoz Pharmaceuti cals for supplying the BS 100-141

REFERENCES

1 Schmitt H Schmitt H., and Fenard S Evidence of alpha sympathomimetic component in the inhibitory effects of catapresan on vasomotor centers antagonism by Piperoxan Europ J Pharmacol. 13 208 1971

2 Saameli K Scholtysitk, G and Waite R Pharmacology of B S 100 141 a central acting anti hypertensive drug Clin Exp Pharmacol. Physiol (Suppl) 2 207 1975

3 V A Cooperative Study on Antihypertensive Agents E D Freis Chairman A double blind control study of antihypertensive agents, Arch. Intern Med. 106 133 1960

4 Turner A S A study of N amidino-2 (2,6-dichlorphenyl) acetamide hydrochloride in arterial hypertension Sev enth World Congress of Cardiology Buenos Aires, Abstract

5 Scholtysik, G and Jerie P Pharmacological and clini cal effects of B S 100-141 a new antihypertensive agent, in New Antihypertensive Drugs A Scriabine and Ch. Sweet editors Philadelphia 1976 Spectrum Publica tions

6 Dubach, U C Huwyler R., Radielovic P and Singeisen M A new central acting antihypertensive agent Guanfacine (B S 100-141) Arzneim Forsch. 27 674 1977

7 Jaattela, A Clinical efficacy of B S 100-141 in essential hypertension Europ J Clin Pharmacol. 10 69 1976

The effect of hemodilution with stroma-free hemoglobin and dextran on collateral perfusion of ischemic myocardium in the dog

G P Biro M D Ph D
D Beresford Kroeger B Sc
Ottawa Ontario Canada

The area of ischemia following the sudden occlusion of a major coronary artery is composed of a core ischemic area and a surrounding marginal zone In the former blood supply is minimal and unless flow is restored rapidly irreversible ischemic damage follows In the marginal zone however potentially adequate collateral blood flow may exist and appropriate interventions designed to alter the balance of oxygen supply and demand may ensure survival of this zone[1] Salvage of this marginal zone to minimize the mass of subsequently infarcting myocardium has great prognostic significance both in relation to complications in acute phase and in relation to the longer term effects of a subsequent ischemic event[2] Consequently the aim of most therapeutic interventions in the acute phase is to salvage the marginal zone

Perfusion of the marginal zone through collateral vessels is limited by the available pressure gradient and by local vascular resistance Since it is probable that collateral vessels are maximally dilated flow under the prevailing pressure gradient is limited by blood viscosity Since blood viscosity is primarily a function of the hematocrit[5] and since blood viscosity appears to increase early in myocardial infarction in man and in the dog it would be anticipated that hemodilution the reduction of the hematocrit and thereby of blood viscosity may be beneficial and may improve perfusion of the marginal zone through the available collateral channels The available experimental evidence indicates that following hemodilution with dextran collateral flow to the marginal zone is in fact increased[11] and that the severity of ischemic injury is not aggravated[1] or even ameliorated[1] The most important disadvantage of hemodilution however is the proportional dilution of oxygen capacity and content Thus while hemodilution may improve flow it is not clear whether this can offset the attendant reduction in oxygen content In fact Kleinman and colleagues[11] demonstrated an impairment of oxygen supply especially to the subendocardium by the collaterals during hemodilution with dextran

It has been demonstrated that a solution of stroma free hemoglobin (S F H) can be administered without the complications seen with massive in vivo hemolysis[1] Hemodilution with S F H produces a reduction in blood viscosity comparable to that produced by similar dilution with dextran but permits the transport of substantially more oxygen in the plasma phase It was also shown that in the normal heart hemodilution with S F H was followed by marked increase in coronary blood flow favouring the subendocardial layers Furthermore the same procedure appears to prevent the rise in blood viscosity seen in the early phase of myocardial ischemia in the dog These findings suggest a further possibility in the salvage of ischemic myocardium that of achieving the viscosity reducing effects of hemodilution with an agent capable of transporting significant amounts of oxygen Accordingly the present experiments

From the Department of Phy logy Fa ulty f H alth Sci nces Un ersity of Ottawa Ott w O t n C nada

These e periments w re condu ted w th fin n ial support provided by the Medical Research Coun il of C n da grant N MA 4812

Recei ed for publication Sept 1 19 8

Accepted for publication Jan 1 19 9

Reprint requests Dr G P Biro D pt f Ph l F ulty of Health Sciences Uni ersity of Ottaw Nich l St Ott wa Ontario K1N 9A9 Canada

000 -8 03 80/010064 + 12$01 20/0 © 1980 The C V Mosby Co

were undertaken to assess the short term effectiveness of hemodilution with S F H in improving oxygen supply to the marginal zone of ischemic myocardium following an acute coronary occlusion

Methods

The experiments were performed on 26 male mongrel dogs (weight range 13 6 to 26 8 kilograms) under Nembutal (30 mg /Kg) anesthesia The *protocol* consisted of the following the surgical preparation (see below) was followed by a 30 minute period to allow the attainment of a stable cardiovascular state The experiment proper was begun with an initial control period when measurements were obtained this was followed immediately by induction of myocardial ischemia when the previously placed snare was tightened on the left anterior descending coronary artery During the next hour measurements were made at intervals At the conclusion of the measurements at the one hour post occlusion period a rapid exchange transfusion was performed blood was removed by the femoral artery (30 to 35 ml /Kg) and an equivalent volume was reinfused into the femoral vein In nine dogs S F H was infused in another nine dogs their shed blood was returned and in a further six dogs 6% dextran 70 was given in the same manner This divergence in the protocol resulted in three groups Group I comprised the test group of animals subjected to the exchange with S F H those in Group II served as the control subjected to a sham exchange with their own blood and Group III comprised a further control series subjected to hemodilution but without the ability to transport significant oxygen in the plasma phase During the subsequent two hours measurements were made at intervals in all three groups which were treated in an identical manner

The *surgical procedure* was also identical in all animals Catheters were placed in both femoral arteries and veins (one of these was advanced to the pulmonary artery) The chest was opened on both sides in the fifth intercostal space care being taken to effect hemostasis with electrocautery On the left side a short polyethylene catheter was placed in the left atrium and a catheter tip pressure transducer (Millar Instruments Micro Tip PC 350A) was inserted in the left ventricular cavity through the apex A loose ligature was placed about the left anterior descending coronary artery beyond its first septal branch On the right side a catheter was inserted in the coronary sinus and fixed so that its tip lay 2 cm from the valve of the coronary sinus This placed it downstream to all important tributaries

Table 1 The composition of the S F H solution used in the experiments in Group I

Total hemoglobin	8.1 g /dl
Methemoglobin	5% of total pigment
Sodium	132 mEq /L
Potassium	2.5 mEq /L
Chloride	95 mEq /L
Calcium	5 5 mEq /L
Magnesium	1 7 mEq /L
pH	7 17
O_2 capacity	10 2 ml /dl
Total osmolarity	278 mOsm /Kg
Bacterial growth	–

During the whole subsequent experiment the animals were ventilated through a cuffed endotracheal tube with room air using a Harvard respiratory pump with an expiratory resistance of 4 cm H_2O The rate and volume of ventilation were adjusted at the beginning of each experiment to maintain pO_2 and pCO_2 in arterial blood within the physiological range

The following hemodynamic variables were recorded periodically on an Electronics for Medicine VR 6 Simultrace recorder phasic arterial blood pressure phasic left ventricular pressure and its derivative (dP/dt) Lead II of the surface ECG The cardiac output was determined by dye dilution using indocyanine green dye and a Waters densitometer (D400)–cuvette (XC302) system Calibrations were performed with the dog s own blood with and without SFH and dextran as appropriate Calculations were made on a Wang 600 programmable calculator

Blood samples were drawn anerobically from the arterial and coronary sinus catheters at intervals In these samples pO_2 pCO_2 and pH were determined with an IL 113 Blood Gas Analyzer (Instrumentation Laboratories) at 37° C The measured values were corrected using standard nomograms[1] The O_2 content was also determined in these samples using a LEX O CON TL (Lexington Instruments) oxygen analyzer Arterial blood samples were used for the determination of hemoglobin concentration in whole blood and in the plasma phase (by the cyanmethemoglobin

Table II Blood parameters (mean ± SEM) measured in arterial blood in Group I before and after coronary occlusion and after the exchange transfusions

	Pre-occlusion	*Post occlusion*		*Post S F H hemodilution*	
	Control 0′	*30′*	*60′*	*30′*	*60′*
Arterial blood					
pO	84 1 ± 6 7	76 0 ± 8 1	77 7 ± 7 1	80 0 ± 9 9	78.3 ± 8.5
pCO	32.2 ± 1 0	34 4 ± 1 0	35 3 ± 1 4	37 7 ± 1 8	39 7 ± 2 6 †
pH	7 37 ± 03	7 35 ± 04	7.35 ± 02	7.33 ± 02	7.31 ± 03 †
O content	20.2 ± 0 6	20 0 ± 0 5	20 4 ± 0 4	14 6 ± 0 6 †	14 7 ± 0.8 †
O saturation	87 1 ± 6.5	89 0 ± 6.2	88 2 ± 7 0	79 0 ± 7 7	86 4 ± 8.5
[HGB] whole blood	17 1 ± 1 0	16 5 ± 1 0	16 4 ± 0 7	12 0 ± 0 8 †	12.2 ± 1.3 †
plasma	0.2 ± 0.2	0 3 ± 0 1	0.3 ± 0 1	3 7 ± 1 9 †	3 3 ± 1.8 †
Hct	49 ± 3	49 ± 2	50 ± 2	28 ± 2 †	27 ± 1 †
O capacity					
whole blood	23 1 ± 0.8	22 4 ± 1.2	23.3 ± 0 9	18.5 ± 1.2 †	17 0 ± 1 1 †
plasma	0 6 ± 0 1	0 6 ± 0 1	0 6 ± 0 1	4.9 ± 0.2 †	4 6 ± 0.2 †

Indicates statistically significant change ($p < .05$) by paired t test from the pre-occlusion control value
†Indicates statistically significant change ($p < .05$) by paired t test from the 60 minute post occlusion value

Table III Blood parameters (mean ± SEM) measured in arterial blood in Group II before and after coronary occlusion and after the exchange transfusions

	Pre-occlusion	*Post-occlusion*		*Post-exchange*	
	Control 0′	*30′*	*60′*	*30′*	*60′*
Arterial blood					
pO	83.2 ± 5 7	78 0 ± 9 1	80.2 ± 8 1	81 6 ± 7.9	80 6 ± 6 4
pCO	34.2 ± 1 6	35 7 ± 1.5	35 9 ± 1 7	36 1 ± 1 3	35.9 ± 1 7
pH	7.35 ± 05	7.34 ± 03	7.34 ± 04	7 33 ± 06	7.34 ± 05
O content	19 6 ± 0.9	19 1 ± 0 7	20 1 ± 0.5	19.5 ± 0 8	19 0 ± 0 9
O saturation	90 0 ± 7 1	85 7 ± 8 1	91 1 ± 7 6	90 6 ± 6.3	88.5 ± 6 7
[HGB] whole blood	16 4 ± 1 1	16 7 ± 1.3	16 6 ± 1 1	16 1 ± 1.3	15 9 ± 1 4
plasma	0.2 ± 0 2	0.2 ± 0 1	0.3 ± 0 1	0.3 ± 0 1	0 4 ± 0 1
Hct	48 ± 3	48 ± 3	50 ± 2	48 ± 2	47 ± 1
O capacity					
whole blood	21.8 ± 1 1	22 2 ± 1.3	22 1 ± 1 1	21 5 ± 1 6	21 3 ± 1.5
plasma	0.5 ± 0 1	0 4 ± 0 2	0 4 ± 0.2	0 6 ± 0 1	0 7 ± 0 2

method) the hematocrit (by capillary method) and the oxygen capacity of whole blood and of the separated plasma phase Separate arterial and coronary sinus samples were drawn into chilled syringes for the determination of creatine phos phokinase activity

Myocardial blood flow and its distribution were estimated from the trapping of radionuclide labelled microspheres (15 ± 3 μm) (3M Co) These were prepared and injected into the left atrium according to procedures developed by others Microspheres labelled with Yb were injected in the pre occlusion control period those labelled with Cr were injected one hour after the occlusion and those labelled with Sr^{85} were injected one hour after the exchange transfusion Absolute and relative blood flow calculations were made using arterial reference samples[9] drawn during and after the injections At the conclusion of the experiment the heart was removed separate epicardial and endocardial samples were taken from the visibly ischemic area from the marginal zone and from the normal regions These tissue samples were digested in 4N KOH for 48 hours Radioactivity was determined in the digested samples in a Packard two channel gamma spectrometer (3002) using three passes at settings previously deter

Table IV Blood parameters (mean ± SEM) measured in arterial blood in Group III before and after coronary occlusion and after the exchange transfusions

	Pre-occlusion	*Post-occlusion*		*Post dextran hemodilution*	
	Control 0'	30'	60'	30'	60'
Arterial blood					
pO	87 1 ± 5 6	84 1 ± 6 7	83.2 ± 5.9	84 1 ± 6.2	85 0 ± 5.9
pCO	34 1 ± 1 6	35.2 ± 1 1	35 4 ± 1.3	35 1 ± 1 1	35.2 ± 1 4
pH	7.36 ± 04	7.35 ± 06	7.34 ± 06	7.32 ± 05	7.32 ± 04
O content	19.8 ± 0.9	19 1 ± 0.8	18.8 ± 1.2	10.9 ± 1 1	9.8 ± 0.9
O saturation	89 7 ± 5 8	88 0 ± 6 1	85.3 ± 5.8	91.8 ± 6 7	91.9 ± 6 1
[HGB] whole blood	16.5 ± 1 1	16.3 ± 1.3	16 4 ± 1.2	8 9 ± 1 6	8 0 ± 1.5
plasma	0.2 ± 0 1	0.2 ± 0.2	0.3 ± 0 1	0.3 ± 0.2	0 4 ± 0.2
Hct	48 ± 4	49 ± 7	49 ± 2	26 ± 3	24 ± 3
O capacity whole blood	21.9 ± 1 7	21 7 ± 1.5	22 0 ± 1.3	11.9 ± 1 7	10 7 ± 1.3
plasma	0 4 ± 0 1	0.5 ± 0 1	0 5 ± 0 1	0 6 ± 0 1	0 7 ± 0 1

Indicates statistically significant change ($p < .05$) by paired t test from the 60-minute post-occlusion value

mined to minimize spectral overlap Calculations of blood flow were made using a program developed for this purpose on a Wang 600 calculator

The stroma free hemoglobin (S F H) solution used in these experiments was prepared using sterile techniques in a single batch from out of date human packed erythrocytes by the method of Rabiner and co workers[2] A separate batch prepared previously by the same method was tested in rabbits and dogs it was free of pyrogens and only a transient (< 2 min) hypotensive reaction was occasionally seen when administered rapidly in an exchange transfusion (40 ml /Kg) The electrolyte composition of the SFH reflected that of hemodialysis fluid (Formula Q Anachemia Ltd) used in dialysing it The composition is listed in Table I Dextran was prepared from powder form as a 6% solution in Ringer s

In a preliminary series of experiments the ischemic region following occlusion of the LAD artery was delineated in seven dogs This was done by comparison of the stained myocardium after postmortem injection of Toluidine Blue in the aortic root with the distribution of microspheres The visibly ischemic area had a mean flow of 21 ± 4% of the preocclusion value while the marginal zone was 7 ± 2 mm wide on the epicardial surface with a mean flow of 52 ± 6% of the preocclusion value The unaffected myocardium received 127 ± 8% of the preocclusion flow

Statistical analysis was performed on a Wang 600 programmable calculator utilizing paired t tests to detect significant changes within groups and Duncan s multiple range tests to detect differences between groups

Results

1 Pre occlusion control period The dogs comprising the three groups were not different in the preocclusion control period with respect to arterial and coronary sinus blood gas parameters (Tables II to IV and Fig 3) hemodynamic variables (Figs 1 and 2) and myocardial blood flow (Table V) Because of the extensive surgical damage to thoracic muscles CPK activity found in peripheral (arterial) blood was already excessive (range 280 to 370 mU /ml) it was for this reason that we elected to measure CPK difference across the heart and subsequently to calculate CPK *output* using the measured myocardial blood flow as a semiquantitative index of ischemic myocardial damage resulting in leakage of the enzyme

2 Effects of coronary occlusion Occlusion of the LAD artery was *followed* by transient dysrhythmias in only four dogs of these three dysrhythmias subsided spontaneously within five minutes The one experiment with persistent dysrhythmia (runs of VPB s and bigeminy) was discarded All other animals survived until the experiment was terminated three hours or later following the occlusion without any drugs save the supplements of anesthetic as required Qualitatively and quantitatively the changes during the 60 minute period following the occlusion were

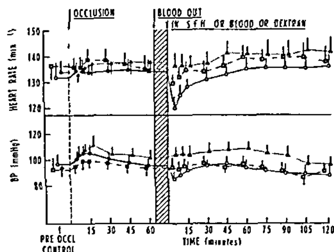


Fig 1 Time course of systemic hemodynamic changes (heart rate and mean arterial blood pressure [mean ± SEM]) following coronary occlusion and following the exchange tran fusions *Circles* indicate Group I hemodiluted with SFH solution *squares* indicate Group II reinfused with whole blood *triangles* indicate Group III hemodiluted with dextran 70 For details see text

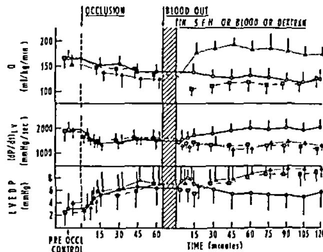


Fig 2 Time course of changes in left ventricular parameters (cardiac output dP/dt and end-diastolic pressure mean ± SEM) following coronary occlusion and following the exchange transfusions Symbols as in *Fig 1*

essentially similar in the three groups Arterial blood pO_2 fell in all three groups but only in Group I did the fall attain statistical significance by paired t test ($p < 05$) similar though smaller changes in the opposite direction were observed in arterial blood pCO

In terms of hemodynamic variables similar trends were evident in all three groups (Figs 1 and 2) while heart rate remained constant mean rterial pressure tended to rise Group III s pres doing so to the greatest extent Cardiac output and stroke volume tended to fall while left ventricular end diastolic pressure rose None of these changes was statistically significant A consistent decrease was evident in L V dP/dt of approximately 25% this decrement was signifi cant in all three groups at the 15 minute period All three groups exhibited a fall in coronary sinus pO_2 and oxygen saturation (Fig 3) of approxi mately 3 to 4 mm Hg and 5 to 6% respectively The levels attained were approximately equal at the 30 and 60 minute post occlusion periods At the latter time CPK difference across the heart widened significantly (Table VI) and calculated CPK output by the heart increased seven to eightfold ($p < 05$) in all groups

Estimated blood flow to the normal myocar dium (Table V) at one hour post occlusion was elevated it was significantly increased ($p < 05$) to both endocardial and epicardial layers in Groups II and III and only to the epicardial layer in Group I Blood flow to the endocardial layers of the ischemic zone was reduced to approximate ly 32% ($p < 05$) of the preocclusion value while epicardial flow was 37 to 40% of the control value The transmural flow distribution was significant ly reduced in Group I only (endo/epi flow ratio = 0 83 ± 07) in contrast to Groups II and III (endo/epi ratios of 0 89 ± 11 and 0 93 ± 09 respectively) Perfusion of the marginal zone was somewhat better than that of the ischemic zone at this time mean endocardial flow ranging from 36 to 40% and mean epicardial flow ranging from 39 to 49% of the respective control values The transmural distribution of flow was significantly reduced in Group I only (1 06 ± 07 to 0 80 ± 10 $p < 05$)

3 Effects of the exchange transfusions The three different types of exchange transfusion produced significant differences between the three groups in terms of oxygen parameters in arterial blood (Tables II to IV) The hematocrit was reduced to 26 to 28% in Groups I and III while it remained at about 48% in the blood control group (Group II) In spite of the approxi mately equal hematocrit Groups I and III differed in terms of O_2 capacity and content in the plasma phase in the former O capacity was nearly 5 ml /dl in contrast to that in Group III (approximately 0 6 ml /dl) As a result of the oxygen carried in the plasma phase total O content in arterial blood was about 4 ml /dl higher in Group I than in Group III although it was still 5 ml /dl lower than in the undiluted blood of Group II In other respects blood

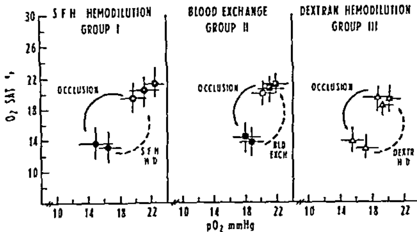


Fig 3 Changes in coronary sinus pO and O saturation (mean ± SEM) in the three groups *Open symbols* indicate the values in the pre-occlusion control state *filled symbols* are those obtained at 30 and 60 minutes following coronary occlusion and the *half filled symbols* are those values obtained at 30 and 60 minutes after the exchange tran fusions

Table V Myocardial blood flow (ml /g /min) (mean ± SEM) measured by microspheres in the three groups before and after coronary occlusion and after the exchange transfusion in different regions of the heart

Period	*Pre occlusion control*			*1 hr post-occlusion*			*1 hr post-exchange*		
Group	*I*	*II*	*III*	*I*	*II*	*III*	*I*	*II*	*III*
Ischemic zone									
Endo	1 12 ± ?1	1.28 ± .23	1 19 ± 1"	0.21 ± 19	0.34 ± .31	0 3" ± 1"	0 64 ± 13	0.38 ± .09	0.59 ± 12
Epi	1 04 ± 14	1 19 ± 17	1 07 ± 20	0 2" ± .20	0 40 ± 14	0 40 ± .20	0 61 ± 14	0 44 ± 10	0 63 ± 1"
Endo/epi ratio	1 08 ± 09	1 09 ± 11	1 12 ± 09	0 83 ± 07	0 89 ± 11	0.93 ± .09	1 04 ± 12	0.89 ± 13	0.94 ± 11
Marginal zone									
Endo	1 1" ± 16	1.23 ± 18	1.29 ± .21	0 43 ± 13	0 48 ± .20	0.52 ± 14	0 81 ± 12†	0.5_ ± 1"	0 61 ± 15
Epi	1 10 ± 27	1 14 ± .24	1.22 ± .23	0.54 ± 10	0 47 ± 13	0 48 ± 13	0 6" ± 11†	0 59 ± 12	0 69 ± 1"
Endo/epi ratio	1 06 ± 09	1 09 ± 09	1 06 ± 11	0 80 ± 10	1 0_ ± 09	1 05 ± 09	1.21 ± 14	0.88 ± 13	0.88 ± 11
Normal zone									
Endo	1.27 ± 14	1.38 ± 19	1 31 ± 2?	1 48 ± 15	1.85 ± 11	1 "8 ± 17	2 6" ± 19	1 "8 ± 19	2 "9 ± 13
Epi	1.21 ± 17	1.32 ± .21	1 09 ± 1/	1.54 ± 17	1 66 ± 08	1.34 ± .21	3 71 ± 11	1 71 ± .17	2 64 ± 16
Endo/epi ratio	1 05 ± 14	1 05 ± 09	1.20 ± 14	0.96 ± 09	1 11 ± 08	1.33 ± 10	0.99 ± 09	1 04 ± 0"	1 06 ± 05

Indicates statistically significant ($P < .05$) change by paired t test from the pre-occlusion valu
†Indicates st tsti lly significant ($p < 05$) ch nge by paired t test from th 60 minute post-occl sion alue

Table VI Comparison of arterial coronary sinus C P K differences and calculated CPK output at various times in the three groups

Group	*Aortocoronary sinus C.P K Δ (mU /ml)*			*C.P.K output (mU /g heart ut /min.)*		
	I	*II*	*III*	*I*	*II*	*III*
Pre occlusion	7 2 ± 4 1	8 1 ± 3 2	7 9 ± 4 3	8 7 ± 3 0	9 7 ± 4 9	9.5 ± 3 7
30 post-occlusion	27 ± 6	32 ± 7	37 ± 9			
60 post occlusion	47 ± 10	51 ± 11	46 ± 12	70 5 ± 12 1	68 8 ± 14 1	"8.2 ± 17 1
30 post-exchange	31 ± 14	67 ± 15	4" ± 14			
60 post exchange	2? ± 9	71 ± 19	ı0 ± 13	5?.9 ± 9 1	121 ± 29†	152 ± 31†

$p < 05$ by paired t test from pr oc lus on co trol.
†$p < 05$ by p ired t test from 60 m nut po t oc lu on al e

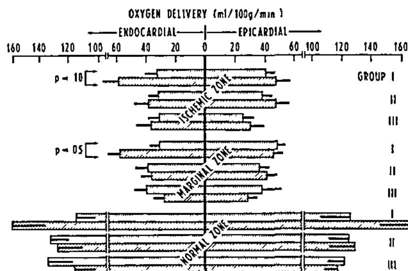


Fig 4 Summary of the changes (mean ± SEM) in myocardial oxygen delivery in the three experimental groups For the sake of simplification the pre occlusion values were omitted *stippled bars* indicate the measurements made at 60 minutes post occlusion while the *cross hatched bars* indicate the measurements made at the 1 hour post infusion (i e 2 hours post occlusion) period Note the statistically significant increase in subendocardial O delivery in the marginal zone in Group I Note break in scale to accommodate higher values in the normal zone

parameters were similar in the three groups

In hemodynamic terms (Figs 1 and 2) only two significant trends were evident between the groups Firstly only Group III subjected to dextran hemodilution exhibited elevated ($p < 05$) cardiac output when compared to the other groups Secondly Group I exhibited a significantly raised dP/dt as compared to the post occlusion depressed levels but only at two of the measurement periods Two minor and not atistically significant differences were also vident Group I showed the most marked fall in arterial blood pressure and the lowest LVEDP

The effects of the exchange transfusions on blood parameters in the coronary sinus are summarized in Fig 3 Surprisingly a rise of approximately equal magnitude in pO and O_2 saturation occurred in all three groups returning these parameters to within the preocclusion range This was an unexpected finding in at least Group II

Blood flow to the normal myocardium (Table V) rose only marginally in Group II while it increased significantly ($p < 05$) in both hemodiluted groups (Groups I and III) These increments were of such magnitude that the calculated O delivery was maintained at essentially the control level In contrast in the ischemic and marginal zones although there were significant increments in blood flow (Table V) O_2 delivery was restricted (Fig 4) in all three groups with two notable exceptions in Group I endocardial O delivery after hemodilution with SFH was nearly significantly ($0 10 > p > 05$) higher in the ischemic zone and it was significantly ($p < 05$) higher in the marginal zone when compared to the pre hemodilution level in the same animals as well as when compared to the post exchange transfusion values in the other groups The data indicate a significant improvement in endocardial perfusion following hemodilution with SFH in the normal as well as in the ischemic myocardium

One hour following the exchange transfusion the washout of CPK from the heart (Table VI) increased significantly in Groups II and III but was reduced in Group I although the decrement itself in the latter group did not attain significance in itself ($p = 10$) the numerical value in Group I was significantly ($p < 05$) lower than those found at the same time in the other groups The weights of the three zones of myocardium prior to their digestion in KOH are compared in Table VII Since the mean values of the total left ventricular weights were somewhat different in the three groups comparison on a percentage basis indicates that the ischemic and marginal zones were somewhat smaller in Group I This may indicate an apparent underestimation of these zones because of a difficulty in visual

Table VII Weights of the three zones of myocardium in the three groups

	Group I	*Group II*	*Group III*
Ischemic zone			
Weight	159 ± 17 g	253 ± 14 g	21.9 ± 31 g
% of whole LV	148 ± 14%	223 ± 09%	181 ± 26%
Marginal zone			
Weight	64 ± 19 g	88 ± 07 g	97 ± 1.2 g
% of whole LV	54 ± 17%	74 ± 06%	80 ± 10%
Normal zone			
Weight	91.8 ± 112 g	80.5 ± 100 g	897 ± 107 g

demarcation in the animals hemodiluted with SFH This is reflected in the somewhat lower blood flow (especially in the endocardial layer) found in the ischemic zone in this group at the one hour post occlusion period indicating that this zone may have been underestimated in comparison with the other groups

Discussion

A solution of hemoglobin would have many of the characteristics of a potentially ideal plasma expander or blood substitute colloid osmotic effects oxygen transporting and releasing capability stability in storage greater than that of whole bank blood absence of type specific and non specific antigens and of viral contaminants Over the past half century a number of attempts have been made to produce suitable hemoglobin solutions [3] with limited success More recently the undesirable side effects (impaired coagulation and renal function) have been shown to be largely due to stroma fragments and their removal eliminated most of these effects [6] The potential usefulness of stroma free hemoglobin solution was illustrated by Moss and associates who demonstrated that apparently bloodless baboons could survive a complete exchange transfusion with a hematocrit of less than 3%

The rationale for the hypothesis tested in the present experiments can be appreciated against the following background it is now increasingly recognized that the rheological properties of blood play a pivotal role in determining nutritive capillary flow These rheological properties are mainly determined by the hematocrit and the physical conditions of flow The viscosity of whole blood is related to the hematocrit in an apparently exponential manner so that a given increment in hematocrit produces increasingly greater rises in viscosity as the initial hematocrit increases This is partly due to the fact that erythrocytes increasingly tend to aggregate forming larger and less easily deformed particles as the hematocrit increases The tendency to aggregation is opposed by the shearing forces to which blood is subjected during flow the extent of disaggregation is primarily a function of the prevailing shear rate At the relatively low shear rates prevailing in the microcirculation especially during conditions of a reduction in the driving pressure gradient and flow (e g hypotension or coronary artery stenosis), the tendency to aggregation becomes dominant and a vicious circle of increasingly impaired nutritive perfusion of the microcirculation follows

Under a given set of prevailing conditions (perfusion pressure vascular hindrance shear rate) in a given vascular bed the resistance to blood flow is a direct function of blood viscosity Thus collateral perfusion in the absence of autoregulation would be largely determined by blood viscosity Clinical studies in patients with fresh myocardial infarction have demonstrated increased blood viscosity and significant deterioration in rheological properties of blood Under controlled experimental conditions a significant and progressive rise in blood viscosity occurs within one hour of a sudden coronary occlusion in the dog This renders the observable collateral perfusion of the ischemic myocardium less than optimal and a reduction in blood viscosity appears desirable Hemodilution with SFH was shown not only to reduce the blood viscosity in proportion to the reduction in hematocrit but to produce a blocking effect of the rise in observed viscosity and erythrocyte aggregation accompanying acute myocardial ischemia This combination of rheological effects with the oxygen

transporting and releasing capacity of S F H and its effects on improving subendocardial perfusion in the non ischemic heart[16] have lead to the present experiments

Two other characteristics of S F H must be considered namely its short intravascular retention and its high affinity for oxygen Unprotected by the erythrocyte membrane the unaltered hemoglobin molecule in solution in the plasma disappears fairly rapidly from the circulation its half life in the dog is 2 to 3 hours[4] It is for this reason that our experiments were of short duration only The benefits however, could be sustained by a continuous infusion Secondly in the absence of the intraerythrocytic regulators of hemoglobin oxygen affinity[43] S F H releases its oxygen less readily than erythrocytic hemoglobin[1 3 44] This would appear to be a disadvantage However the relatively hypoxic and acidotic environment of ischemic myocardium would be expected to induce O release from plasma phase hemoglobin as well

The quantitative estimation of the mass of ischemic myocardium is difficult The most successful estimator is that pioneered by Sobel and co workers utilizing the estimation of total C P K released For a variety of practical reasons this was not possible in our experiments Our results also illustrate a variety of obvious difficulties The choice of the dog as experimental animal may be questioned because of its extensive and variable coronary collateral circulation Yet this animal is the most frequently used model in this area We tried to avoid any bias by the random assignment of animals to the three treatment groups There was also obvious difficulty in the precise visual demarcation of the ischemic and marginal zones It appears that these zones were under estimated in Group I Clearly this difficulty and the heterogeneity of myocardial perfusion contributed to the differences between the groups The underestimation of the ischemic zone in Group I resulted in comparison of a more ischemic core with a more restricted collateral perfusion than those in Groups II and III Nevertheless subendocardial O delivery in the former was significantly improved by hemodilution with S F H

In spite of these difficulties the experiments revealed three lines of circumstantial evidence pointing to an improved collateral perfusion of the marginally ischemic myocardium particularly to the subendocardial layers following hemodilution with S F H Firstly Group I exhibited the greatest increment in subendocardial blood flow and in O delivery Secondly in contrast to the increasing output of C P K in Groups II and III there was a reversal of this trend in Group I Presumably this indicates a reduction in the mass of myocardium leaking the enzyme Although the majority of C P K measurable in peripheral blood gets there by way of the cardiac lymph the actual estimation of direct washout of this enzyme by the collateral blood flow must bear some relation to a mass intensity product of myocardial damage Thirdly, although statistically not consistently significant Group I exhibited the best left ventricular performance returning to the pre occlusion level While a strict linear relationship between the extent of myocardial ischemia and performance may not exist some correlation has been demonstrated[47 4] and it is reasonable to expect that the extent of functional limitation is related to the mass of ischemic myocardium

There is a further possibility of a passive mechanical factor contributing to the improved collateral perfusion Flow in maximally dilated vessels as these collaterals presumably are is also proportional to the left ventricular end diastolic pressure because of the vascular waterfall phenomenon[50] As a result of the lower end diastolic pressure in Group I there is less compression than in the other groups allowing better perfusion through the maximally dilated collaterals The fact that a similar phenomenon is not seen in the Dextran hemodiluted group (Group III) suggests that a factor other than reduced impedance to ejection is also involved

Blood parameters measured in the coronary sinus revealed no significant differences between the groups The pO and oxy hemoglobin saturation in coronary sinus blood reflects the integrated effects of a spectrum of oxygen extraction by various regions of the myocardium Because of the shape of the oxy hemoglobin dissociation curve hyperperfused areas tend to dominate the effects of hypoperfused areas The initial decrease in coronary sinus pO following the occlusion reflected the low pO_2 of the blood draining from the poorly perfused areas The subsequent rise in pO_2 in all the groups appears to

reflect two effects redistribution of myocardial flow with increased perfusion of the normal myocardium and a subsequent improvement with time in collateral perfusion of the ischemic myocardium Although the normal myocardium assumes the work share [1] and oxygen cost of the ischemic regions the increased flow to the normal myocardium may have permitted a rise in pO_2 and O_2 saturation of the blood draining from these regions thereby diluting the relatively small volume of low pO blood draining from the ischemic regions A second possibility is that of a spontaneous improvement with time in collateral perfusion of the ischemic myocardium and a rise in oxygen saturation and pO in the blood draining therefrom This possibility is only partly supported by the flow measurements in Group II although there was no significant increase in blood flow to the ischemic core there was in fact a modest flow increment (26%) in the epicardial layers of the marginal zone Similar changes in coronary sinus blood were seen in the other groups as well but it is not quite clear what mechanism accounts for the observed changes and they may not necessarily reflect changes in tissue pO_2 in the different regions of the heart

It appears that these findings based on an expectation of rheological improvement are suggestive of some improvement in collateral perfusion of the ischemic myocardium This would warrant further experimental exploration of the possible therapeutic benefits of hemodilution with S F H

Summary

The effect of hemodilution with stroma free hemoglobin (SFH) solution was assessed on the collateral perfusion of acutely ischemic myocardium in anesthetized dogs A similar protocol was used in three groups one hour following occlusion of the LAD coronary artery a rapid exchange transfusion was performed and the changes were followed for the subsequent two hours Group I was hemodiluted with SFH in Group II whole blood was reinfused and Group III was hemodiluted with dextran 70 Following the exchange transfusions blood flow to the ischemic zone (15 ± 3 μm microspheres) increased in all groups but only marginally so in Group II (23 ± 17%) The greatest increments were seen in the SFH hemodiluted group (Group I) in which endocardial flow increased by 83 ± 29% ($p < 05$) and epicardial flow increased by 45 ± 21% these resulted in the greatest improvements in oxygen delivery Significant increments in blood flow were seen in Group III as well but oxygen delivery was less adequate Group I also exhibited the lowest output of CPK from the heart and was the only one in which indices of left ventricular performance (dP/dt and EDP) were returned to the pre occlusion level These findings suggest the possibility that reduction of blood viscosity by dilution with SFH improves collateral perfusion of the ischemic myocardium

We are deeply grateful to Drs. M B Perry and S Martin the National Research Council Ottawa for their valuable advice and for generously allowing us to use some of their equipment during the preparation of S F H solution We wish to thank Dr D Whitaker Department of Biochemistry University of Ottawa for permission to use his flow through centrifuge and Mr R Monaghan for his assistance as well as Dr R Couture Department of Medicine Ottawa General Hospital, for permission to use the facilities of the Hemodialysis Unit and Mr T Rafter for his valuable assistance Dr G Rock, Director Ottawa Branch Canadian Red Cross Blood Transfusion Service kindly made available to us out-of-date packed cells

Note added in proof

In the interval following submission and acceptance of this paper another report has appeared (Feola M Azar D and Wiener L Improved oxygenation of ischemic myocardium by hemodilution with stroma free hemoglobin solution Chest 75 369 1979) reporting essentially similar findings These authors observed that a similar procedure of hemodilution with S F H resulted in improvement in myocardial tissue p0 and a reduction in the presumptive infarct volume when compared to that seen following hemodilution with dextran or the reinfusion of whole blood This and the present paper are thus in substantial agreement on the apparently beneficial effects of this procedure upon myocardial ischemia

REFERENCES

1 Jennings, R B and Reimer K A Salvage of ischemic myocardium Mod Concepts Cardiovasc Dis 53 125 1974
2 Sobel B E Bresnahan G F., Shell W E., Yoder R D Estimation of infarct size and its relation to prognosis Circulation 46 640 1972
3 Epstein S E., Kent K M Golstein R E., Borer J S and Redwood D R Reduction of ischemic injury by

nitroglycerin during acute myocardial infarction N Engl J Med. 292 29 1975

4 Guyton, R. A., and Daggett, W. M. The evolution of myocardial infarction physiological basis for clinical intervention, in International Review of Physiology II, vol. 9 pp 305-339 Baltimore 1976 University Park Press

5 Begg, T. B., and Hearns J. B. Components in blood viscosity. The relative contribution of haematocrit plasma fibrinogen and other proteins, Clin. Sci. 31 87 1966

6. Dintzel, J., Bang H. O., and Thorsen, N. Myocardial infarction and whole blood viscosity Acta Med. Scand. 183.577 1968

7 Jan, K M., and Chien, S Observations on blood viscosity changes after acute myocardial infarction, Circulation 51 1079 1975

8 Biro G P., Early changes in blood viscosity following coronary occlusion in the dog, J Molec. Cell. Cardiol. 11 (Suppl. 1) 7 1979

9 Langsjoen, P H., and Inmon, T W Hemorrheologic observations in acute myocardial infarction Angiology 19:247 1968

10 Yoshikawa, H., Powell, W. J., Jr., Bland, J H L., and Lowenstein, E Effect of acute anemia on experimental myocardial ischemia, Am. J Cardiol. 32 670 1973

11. Johansson, B., Linder E., and Seeman, T Effects of hematocrit and blood viscosity on myocardial blood flow during temporary coronary occlusion in dogs, Scand. J Thorac. Cardiovasc Surg. 1 165 1967

12. Cohn, L. H., Lambert, J. J., Florian A., Moses R., Vandevanter S., Kirk, E., and Collins J J., Jr.. Effects of hemodilution on acute myocardial ischemia J Surg. Res. 18 523 1975

13 Kleinman, L. H., Yarbrough, J W., Symmonds, J B., and Wechsler A. S Pressure flow characteristics of the coronary collateral circulation during cardiopulmonary bypass, J Thorac. Cardiovasc Surg. 75 17 1978

14 Rabiner S F Hemoglobin solution as a plasma expander Fed. Proc 34 1454 1975

15 Usami, S., Chien, S., and Gregersen, M I. Hemoglobin solution as a plasma expander Effects on blood viscosity Proc. Soc Exp Biol. Med. 136 1232 1971

Biro G P., Beresford Kroeger D., and Smith, B N Myocardial oxygen-supply during hemodilution with stroma free hemoglobin and methemoglobin solutions, in Blood Substitutes and Plasma Expanders, edited by G A. Jamieson and T J Greenwalt, New York, 1978 Alan R Liss, Inc., pp 213-222.

17 Kelman, G P., and Nunn, J F Nomograms for correction of blood pO pCO pH and base excess for time and temperature, J Appl. Physiol. 21 1484 1966

18 Rosalki, S B Creatine phosphokinase isoenzymes Nature 207 416 1965

19 Heymann, M. A., Payne, B D Hoffman, J I. E and Rudolph, A. M Blood flow measurements with radionuclide labeled particles, Prog Cardiovasc Dis. 20 55 1977

20 Bartrum R J Berkowitz D M and Hollenberg N K A simple radioactive microsphere method for measuring regional flow and cardiac output Invest Radiol 9 126 1974

21 Rabiner S F Helbert J R Lopas H and Friedman L H Evaluation of a stroma free hemoglobin solution for use as a plasma expander J Exp Med 126 1127 1967

22 Surgenor D MacN and Berzow B D Artificial blood and the national blood policy Fed Proc 34 1518 1975

23 Hamilton, P B., Farr L E., Hiller A and VanSlyke D D Preparation of hemoglobin solutions for intravenous infusion, J Exp Med. 86 455 1947

24 Hamilton, P B., Hiller A., and VanSlyke D D Renal effects of hemoglobin infusions in dogs in hemorrhagic shock, J Exp Med. 86 477 1947

25 Pennell, R. B., and Smith, W E Preparation of stabilized solutions of hemoglobin Blood 4 380 1949

26 Brandt J L., Frank, N R. and Lichtman H. C The effects of hemoglobin solutions on renal function in man, Blood 6 1152 1951

27 Miller J H., and McDonald, R. K. The effect of hemoglobin on renal function in the human, J Clin Invest 30 1033 1951

28 Birndorf N I., and Lopas, H Effects of red cell stroma free hemoglobin solution on renal function in monkeys, J Appl. Physiol. 29 573 1970

29 Relihan M., and Litwin, M S Clearance rate and renal effects of stroma free hemoglobin on acidotic dogs Surg. Gynecol. Obstet. 137 73 1973

30 Peskin G W., O'Brien K., and Rabiner S F., Stroma free hemoglobin solution The "ideal" blood substitute? Surgery 66 185 1969

31 Moss G S., Dewoskin, R., and Cochin, A. Stroma free hemoglobin I Preparation and observations on in vitro changes in coagulation Surgery 74 198 1973

32 Kaplan H R., and Murthy V S Hemoglobin solution a potential oxygen transporting plasma volume expander Fed. Proc 34 1461 1975

33 Moss, G S DeWoskin, R., Rosen, A. L., Levine, H., and Palani, C K. Transport of oxygen and carbon dioxide by hemoglobin-saline solution in the red cell free primate in Blood Substitutes and Plasma Expanders edited by G A. Jamieson and T J Greenwalt, New York, 1978 Allan R. Liss, Inc pp 191 203

34 Messmer K., Sunder Plassmann L., Klövekorn, W P., and Holper K. Circulatory significance of hemodilution rheological changes and limitations, Adv Microcirc. 4 1 1972.

35 Replogle R. L., Meiselman H J and Merrill, E. W Clinical implications of blood rheology studies Circulation 36 148 1967

36 Dormandy J A. Clinical significance of blood viscosity Ann. R. Coll. Surg. Engl. 47 211 1970

37 Messmer K., and Sunder Plassman, L. Hemodilution, Progr Surg. 13 208 1974

38 Chien, S Blood rheology and its relation to flow resistance and transcapillary exchange with special reference to shock, Adv Microcirc 2 89 1969

39 Dintenfass, L. Blood rheology in pathogenesis of the coronary heart diseases, AM HEART J 77 139 1969

40 Dintenfass, L. Viscosity and clotting of blood in venous thrombosis and coronary occlusion Circ Res 14 1 1964

41 Dintenfass, L., Julian, D G., and Miller G E. Viscosity of blood in normal subjects and in patients suffering from coronary occlusion and arterial thrombosis AM. HEART J 71 587 1966

42 Bonhard, K. Acute oxygen supply by infusion of hemoglobin solutions, Fed. Proc 34 1466 1975

43 Finch, C A., and Lenfant C Oxygen transport in man, N Engl. J Med 286 407 1972.

44 Greenburg A. G Elia, C and Levine B Hemoglobin solution and the oxy hemoglobin dissociation curve J Trauma 15:943 1975

45 Lecompte F Sinet M., Azoulay E., Muffat-Joly M and Pocidalo J J Oxygen transport by haemoglobin. A comparison of whole blood, washed erythrocytes and haemoglobin solution Biomed. 23 226 1975

46 Alumada, G Roberts R., and Sobel, B E Evaluation

of myocardial infarction with enzymatic indices, Progr Cardiovasc Dis 58 405 1976
47 Goodyer A V N., Wong B Y and Langou R Effect of regional myocardial ischemia on left ventricular isovolumic contraction Cardiovasc Res 11 299 1977
48 Bleifeld W Mathey D Hanrath P Buss H and Effort S Infarct size estimated from serial serum creatine phosphokinase in relation to left ventricular hemodynamics Circulation 55 303 1977
49 Weishaar R Sarma J S M Maruyama Y Fischer R and Bing R J Regional blood flow contractility and metabolism in early myocardial infarction Cardiology 62 2 1977
50 Downey J M Downey H F and Kirk E S Effects of myocardial strains on coronary blood flow Circ Res 34 286 1974
51 Theroux P., Franklin D., Ross J Jr., and Kemper W S Regional myocardial function during acute coronary occlusion and its modification by pharmacological agents in the dog Circ Res 35 896 1974
52 Vokonas P S Pirzada F A and Hood W B Jr Experimental myocardial infarction XII Dynamic changes in segmental mechanical behaviour of infarcted and non infarcted myocardium Am J Cardiol. 37 853 1976
53 Hagl S Heimisch, W Meisner H., Erben R., Baum M., and Mendler N The effect of hemodilution on regional myocardial function in the presence of coronary stenosis, Basic Res. Cardiol. 72 344 1977

Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978 Therefore all manuscripts must be accompanied by the following written statement signed by one author The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C V Mosby Company in the event the work is published The undersigned author warrants that the article is original is not under consideration by another journal and has not been previously published I sign for and accept responsibility for releasing this material on behalf of any and all co authors Authors will be consulted when possible regarding republication of their material

Rest and exercise hemodynamics in children before and after aortic valvotomy

Garth S Orsmond M B B Ch *
F Blanton Bessinger Jr M D
James H Moller M D
Minneapolis Minn

Valvar aortic stenosis is a relatively common congenital heart lesion presenting in childhood[1] Aortic valvotomy is usually recommended for affected children with symptoms such as angina or syncope or with hemodynamic evidence of moderately severe or severe aortic stenosis

In this study the rest and exercise hemodynamics in a group of children with moderate or severe congenital valvar aortic stenosis are compared before and after aortic valvotomy to determine changes occurring as a result of valvotomy

Materials and methods

Eighteen patients 13 males and five females with valvar aortic stenosis were studied by cardiac catheterization at rest both before and after aortic valvotomy

Aortic valvotomy was performed using cardiopulmonary bypass In 15 patients with bicuspid valves both commissures were incised as far as possible toward the anulus without producing significant aortic incompetence In the two patients with a unicommissural valve only the single commissure was incised In the remaining patient with a tricuspid valve and fused commissures two commissures were incised

The age of the patients at the time of preoperative catheterization ranged from 3 months to 17 years (mean of 10 8 years) Aortic valvotomy was performed from 1 to 5 months following the initial cardiac catheterization (mean of 2 8 months) Postoperative catheterization was performed within 2 years of operation in 16 patients and 3 and 10 years postoperatively in the remaining two patients

Cardiac catheterization was performed with the patient in a fasting state following premedication with phenobarbital and morphine The left heart pressures were measured with a N I H angiography catheter or Statham transducer tipped catheter Right sided pressures were measured using a Goodale Lubin catheter The pressures were recorded on an Electronics for Medicine recorder using a Statham 23db pressure transducer for fluid filled catheters

Cardiac output was determined utilizing the Fick principle In 15 of the patients preoperatively and in each of the patients postoperatively oxygen consumption was measured by collecting the patient s expired air in a Tissot spirometer The expired gas was analyzed for O and CO content Oxygen consumption was calculated by standard methods In the remaining three patients preoperatively oxygen consumption was estimated as 160 c c O /min /M Midway during the measurement of oxygen consumption the left ventricular end diastolic pressure (LVEDP) and peak left ventricular systolic pressure were recorded The catheter tip was withdrawn from the left ventricle into the aorta while the pressure was recorded and measured continuously

During the measurement of oxygen consumption blood samples were withdrawn simultaneously from the pulmonary artery and the aorta Oxygen content (O) of these blood samples was determined either by the Van Slyke method or calculated from determinations of oxygen satura

From The Department of Pediatrics and the Dwan Cardiovascular Learning Center University of Minnesota Minneapolis Minnesota

Received for publication Sept 2? 1978

Accepted for publication Dec 29 19 8

Reprint requests James H Moller Box 44 Mayo Memorial Building Minneapolis Minn 55455

*Present address Primary Childrens Medical Center University of Utah 3?0 1?th Ave Salt Lake City Utah 84103

0002-8 03/80/0100 6 + 11$01 10/0 © 1980 The C V Mosby Co

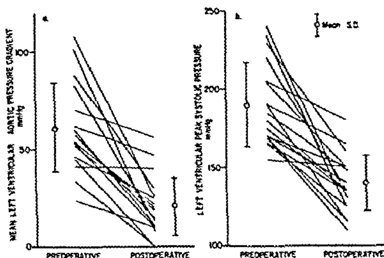


Fig 1 Pre- and postoperative mean left ventricular aortic pressure gradient (*a*) and left ventricular systolic pressure (*b*) at rest

tion hemoglobin and partial pressure of oxygen (pO_2) using the formula $O_2 = 1.36 \times$ hemoglobin $\times$ % saturation $+ 0.003 \times pO_2$ mm Hg

Ten of the 18 patients were exercised both pre and postoperatively on a variable resistance bicycle ergometer at work loads ranging from 30 to 100 watts The work load was chosen so that the patient could continue to exercise for three to six minutes without fatigue and with a heart rate of approximately double the resting heart rate After a constant work load and heart rate had been maintained for several minutes cardiac output was determined by the Fick method and LVEDP left ventricular systolic and aortic pressures were again measured

For both rest and exercise stroke volume was calculated by dividing cardiac output by the heart rate The stroke volume and cardiac output were indexed for body surface area Stroke work index (SWI) was calculated by the formula SWI (gm m/m²) = (SI × 1.055) (LV − LVEDP) × 13.6/1000 where LV = peak left ventricular systolic pressure and SI = stroke index The aortic valve area was calculated from the mean left ventricular aortic gradient and cardiac output was calculated using the formula of Gorlin and Gorlin The aortic valve area was indexed for body surface area

The ratio of the diastolic pressure time interval (DPTI) × arterial oxygen content (O_2) to systolic pressure time interval (SPTI) was used as an indirect measure of subendocardial blood flow For this calculation the left ventricular systolic and diastolic pressure time intervals were calculated from pressure tracings by planimeterization of the superimposed left ventricular and aortic pressure tracings using the method outlined by Lewis and co workers

The presence of aortic insufficiency was evaluated semiquantitatively from cineangiograms recorded after the injection of radiopaque contrast material (1 to 2 c c /kg) into the ascending aorta approximately 2 cm above the aortic valve The degree of aortic insufficiency was graded 1 to 4+ Adequate pre and postoperative aortic cineangiograms were available in 15 of the 18 patients

The comparison of pre and postoperative values for the measured and calculated parameters and the comparison of the resting and exercise data was made by the paired t test

Results

The pre and postoperative data of the 18 patients studied at rest are shown in Table I The pre and postoperative data of ten of the 18 patients studied at both rest and exercise are shown in Table II

Resting hemodynamics The resting heart rate and oxygen consumption before and after aortic valvotomy are not significantly different ($p > 0.1$) indicating that the patients were in comparable resting hemodynamic states at the time of each cardiac catheterization

Although there were no significant differences in the cardiac indices before and after surgery the cardiac indices of individual patients varied No patient had a cardiac index below normal limi

Table 1 Resting hemodynamics

		BSA	*CI*	*HR*	*SI*	*LVEDP*	*LVPSP*	*Mean Gradient*	*AVA*	*SPTI*
1	Pre	1 75	4.3	70	61	13	190	60	0.52	3164
	Post	1.84	2.9	80	36	14	115	11	0 76	259?
2	Pre	1 70	3.9	70	56	12	180	57	0 49	3?76
	Post	1 77	3.2	68	47	12	135	13	0 79	2611
3	Pre	1 13	4.8	80	60	8	170	[illegible]	0 61	3568
	Post	1 65	4 7	96	49	12	140	19	0.84	2957
4	Pre	1 06	3 6	84	42	14	175	59	0 48	3494
	Post	1 06	4 7	80	59	12	135	[illegible]	1 06	25 6
5	Pre	1 0	4.2	72	58	12	170	34	0 74	2980
	Post	1 12	2.9	70	41	11	115	0	—	2541
6	Pre	1 70	3 6	72	50	13	155	53	0 44	3283
	Post	1 73	3.9	66	59	14	150	10	1 16	345?
7	Pre	1.35	5 4	110	49	13	185	45	0.57	3938
	Post	1.53	4 6	120	38	12	148	0	—	2,04
8	Pre	0.92	4.3	96	45	14	190	62	0.50	3610
	Post	1 0	7 1	100	71	13	165	47	0.81	3520
9	Pre	1.51	4.9	78	63	13	165	46	0 67	3463
	Post	1 63	3 7	80	46	16	135	25	0 64	299?
10	Pre	0.94	5.3	100	53	12	170	53	0.53	3400
	Post	1 15	5 1	100	51	11	120	21	0.9?	2600
11	Pre	1 06	3.9	90	43	11	240	89	0.31	4608
	Post	1 10	4.3	78	55	12	130	30	0 72	2738
12	Pre	1 41	6 7	95	70	12	243	101	0.55	3971
	Post	1.52	4.3	90	48	13	128	8	1 16	2880
13	Pre	1 18	3.9	80	49	11	230	83	0.36	4560
	Post	1.23	4 4	78	56	15	160	13	1 1	368?
14	Pre	0.28	4.5	180	25	8	220	108	0.36	6120
	Post	0.66	3.2	90	36	12	135	26	0.52	3096
15	Pre	0 96	4 0	84	48	13	155	24	0 64	3041
	Post	1 03	5 5	104	53	12	125	10	1 6	4160
16	Pre	0.87	7 6	108	70	14	205	70	0 69	380?
	Post	0 96	5.3	90	59	14	180	56	0 63	3744
ı	Pre	0.86	3 6	[illegible]	34	10	170	41	0 41	4200
	Post	1 60	3.2	102	31	10	150	40	0 39	3590
18	Pre	1.30	5.8	100	58	12	210	54	0 64	4640
	Post	1.35	3 8	66	58	18	148	20	0.80	2831
Pre	Mean	1 17	4 7	93	51.9	11.9	189 7	60 6	0.53	3839 9
	STD Dev	±0.37	±1 1	±25 0	±11.5	±1.8	±27.2	±22.3	±0 12	±77? 7
Post	Mean	1.34	4.3	87	49 6	12 9	139 7	20.2	0 87	3048 1
	STD Dev	±0.3?	±1 1	±15 1	±10 4	±1 95	±17 4	±15.2	±0 3	±5?1 4

Pre = preoperat e Post = postoperat e BSA = body surface area M CI = cardiac index L./min./M HR = heart rate beats/min SI = stroke index cc/M LVEDP = left entricular end-diastolic pressure mm. Hg LVPSP = left ventricular peak systolic pressure mm Hg AVA = aortic val e area cm. /m SPTI = ystolic pressure time index mm Hg sec /min DPTI = diastolic pressure time index mm. Hg sec./min O = arterial oxygen content vols % NA = ot ailable

(2 8 L /min /M) in either the pre or the postoperative state The mean resting cardiac index both before the surgery (4 7 ± 1 1 L /min /M²) and after valvotomy (4 3 ± 1 1 L /min /M) was above the expected normal (3 5 ± 0 7 L /min / M)* suggesting that the children were not in a *basal state at the time of cardiac catheteriza*tion

The LVEDP was not significantly altered by surgery Eight patients preoperatively had an LVEDP greater than 12 mm Hg usually to levels of 13 or 14 mm Hg In the other ten patients the LVEDP preoperatively was 12 mm Hg or less In most of the patients only a minor change of 1 to 2 mm occurred following operation and over all *there was no significant change Eight patients* postoperatively had an LVEDP greater than 12 mm Hg including five whose values were greater

DPTI	$\frac{DPTI \times O}{SPTI}$	Aortogram
2772	18	0
2560	20.4	1+
2688	15.2	1+
2448	18.7	2+
2397	12.0	<–1+
2515	14.5	<1+
2755	13.8	0
2488	16.6	0
1800	10.3	NA
2796	17.0	3+
2218	13.5	0
2917	17.8	3+
2332	11.7	1+
1344	11.2	4+
2074	9.1	<1+
2220	9.5	2+
3058	14.7	0
1646	9.3	3+
2080	9.8	0
1920	12.3	2+
2178	7.6	0
2184	12.8	2+
2704	9.5	0
2124	13.5	1+
2976	11.3	<1+
3432	16.4	1+
2160	5.0	NA
2194	11.4	2+
2369	14.0	0
2662	11.4	1+
1642	7.3	0
1656	7.2	1+
2310	9.6	NA
1816	8.2	0
2080	7.8	0
2501	14.4	2+
2338.2	11.1	
±382	3.3	
2769	13.5	
±497.3	3.8	

than 12 mm Hg preoperatively. Three patients (Cases 9, 13, and 18) had a larger increase in the LVEDP after surgery (13 to 16 mm Hg, 11 to 15 mm Hg, and 12 to 18 mm Hg, respectively). The pre- and postoperative resting LVEDP showed no significant correlation with age, left ventricular-aortic mean gradient, or aortic valve area.

The mean left ventricular-aortic pressure gradient was significantly reduced by valvotomy ($p < 0.01$) from a preoperative mean gradient of 60.6 ± 22.3 mm Hg to a postoperative mean gradient of 20.2 ± 15.2 mm Hg (Fig. 1). A similar significant reduction also occurred in peak left ventricular systolic pressure following surgery (Fig. 1).

Although most patients showed a decrease in the resting mean left ventricular-aortic pressure gradient, three of the 18 patients studied at rest (Cases 8, 16, and 17) had only a minor reduction in the resting mean gradient from a preoperative gradient of 62, 70, and 41 mm Hg to a postoperative gradient of 47, 56, and 40 mm Hg, respectively. This indicated significant residual obstruction.

Preoperatively the aortic valve area at rest was less than 0.7 cm²/M² in 17 of the 18 patients (mean of 0.53 ± 0.12 cm²/M²). The remaining patient had an aortic valve area of 0.74 cm²/M² (Case 3). Postoperatively, aortic valve area calculated on the basis of the Fick cardiac output was significantly increased to a mean value of 0.87 ± 0.3 cm²/M² (Fig. 2). Two patients had no residual gradient and so aortic valve area was not calculated. The postoperative valve area, since it is based on cardiac output calculated by the Fick principle, underestimates the valve area in those patients with a significant degree of aortic insufficiency.

In three patients (Cases 14, 16, and 17) the postoperative aortic valve areas were 0.52, 0.63, and 0.39 cm²/M², respectively. These showed minimal change from the preoperative values. Each of these three patients is considered to have major residual stenosis since none had a major degree of aortic insufficiency and the calculated aortic valve area was still small. In patient No. 9 the calculated postoperative aortic valve area was 0.64 cm²/M²; this patient had fairly severe aortic insufficiency and recalculation of the aortic valve area using forward stroke volume based on left ventricular volume studies gave a valve area of 1.12 cm²/M².

The incidence and severity of aortic incompetence increased after aortic valvotomy. Prior to surgery, ten patients had no aortic incompetence noted on aortic angiography. In five others 1+ aortic regurgitation was recognized by cineangiography. In the remaining three patients, although aortic cineangiograms were not performed, there was no clinical evidence of aortic insufficiency. Postoperatively, only two of the 18 patients studied by cineaortography showed no aortic incompetence (Table I). Among the other

Table II Exercise hemodynamics

		HR beats/min		VO cc/min/M²		CI L/min/M		Mean LV Ao gradient		LVPSP mm Hg	
		R	E	R	E	R	E	R	E	R	E
1	Pre	70	120	151	677	4 3	6 6	60	60	190	2?0
	Post	80	140	146	933	2 9	8 0	11	15	11?	160
2	Pre	70	130	192	710	3 9	9 2	57	81	180	?40
	Post	68	120	166	706	3 2	5 9	13	43	135	18?
3	Pre	80	150	171	8?6	4 8	9 6	52	51	1?0	?10
	Post	96	150	146	818	4 7	8 4	19	22	140	180
4	Pre	84	180	160	872	3 6	6 9	59	112	175	2?0
	Post	80	180	166	1034	4 7	8 6	15	42	135	180
5	Pre	72	150	169	762	4 ?	8 4	34	64	170	240
	Post	70	120	167	710	2 9	6 7	0	0	115	160
6	Pre	72	132	169	768	3 6	7 8	53	59	155	200
	Post	66	130	204	783	3 9	9 0	10	0	1?0	160
7	Pre	110	170	173	785	5 4	8 3	45	55	185	2?0
	Post	120	155	211	710	4 6	7 0	0	0	148	185
8	Pre	96	150	148	505	4 3	7 7	62	62	190	240
	Post	100	140	212	602	7 1	10 4	47	60	165	2?0
9	Pre	78	138	164	623	4 9	7 7	46	9?	165	?30
	Post	80	132	154	68?	3 7	6 1	25	37	135	180
10	Pre	100	150	193	768	5 3	8 0	53	95	170	230
	Post	100	155	152	6?2	5 1	7 4	21	28	120	150
Pre	Mean		147	169	734 6	–	8 0	?2 1	73 4	1??	230
	STDDev		±18	±14 9	112 3	–	±0 9	±8.5	±20 9	±11 3	±19 4
Post	Mean		142	172 4	760	–	7 8	16 1	24 7	135	1?6
	STDDev		±18 4	±26 5	±136	–	±1 4	±13 6	±21 0	±16 1	±20 0

HR = heart rat VO = oxygen uptake cc/mn/M CI = cardiac index LV Ao = l ft ventricular aortic LVPSP = left ventricular systolic pressure DPTI = di tolic pressu e time interval SPTI = systol pressure time interval O = arterial oxygen content vols % SWI = stroke work index LVEDP = left ventricula end-diastolic pressure SI = stroke inde AVA = aortic val e area

6[4] the degree of incompetence was assessed as 1+ in six patients 2+ in six patients and 3+ in four patients Two of the four patients with large regurgitant flows had a unicommissural valve at surgery the other two patients had bicuspid valves

DPTI × O /SPTI was calculated to assess indirectly the subendocardial blood flow Of the 18 patients the preoperative resting DPTI × O /SPTI ratio was less than 10 in eight patients and greater than 10 in the other ten patients For the entire group of patients flow ratio at rest correlated inversely with the mean gradient ($r = -0 5$) LV pressure ($r = -0 56$) and heart rate ($r = -0 72$) The flow ratio did not correlate well with the aortic valve area ($r = 0 17$) Following operation only four patients had a DPTI × O_2 /SPTI of less than 10 In three of these patients (Cases 8 16 and 17) the reduced ratio reflected residual obstruction since in each patient the resting left ventricular aortic mean pressure gradient was 40 mm Hg or more after surgery In the fourth patient (Case 9) although the mean gradient was reduced there was a marked increase in the severity of aortic insufficiency For the entire group postoperatively there was a significant increase in the DPTI × O_2 /SPTI from a preoperative mean value of 11 1 ± 3 3 to a postoperative mean value of 13 5 ± 3 8 ($p < 0 01$) (Fig 3) The increase in this ratio is related mainly to the reduction in systolic pressure time interval from a preoperative mean value of 3 839 9 ± 773 to a postoperative mean value of 3 048 ± 521 4 mm Hg sec/min There was little change in the DPTI following surgery decreasing from 2 338 2 ± 382 mm Hg sec/min to 2 269 7 ± 497 3 mm Hg sec/min A slight decrease in DPTI may be related to the increased degree of aortic insufficiency and lowering of aortic diastolic pressure

DPTI		*SPTI*		*DPTI × O / SPTI*		*SWI* gmM/M²/min		*LVEDP* mm Hg		*SI* cc/min/M		*AVA* cm./M	
R	*E*	*R*	*E*	*R*	*E*	*R*	*E*						
2772	2323	3146	5688	18 0	8 6	155.9	163 4	13	18	61	[illegible]	0.52	0 69
2560	2800	2592	4256	20 4	14.5	52.2	118 1	14	18	37	57	–	–
2688	2298	3276	6656	15.2	6 4	135 0	277 2	12	18	56	73	0 49	0 79
2448	2400	2611	4224	18 7	11.9	82.9	116 4	12	16	47	49	–	–
2392	2370	3568	5880	12 0	.2	139.5	180.9	8	13	60	64	0 61	0.92
2515	3000	2957	4680	14.5	11 1	90 0	134.2	12	13	49	56	–	–
2755	2196	3494	6444	13.8	6 0	97 0	142 7	14	15	49	39	0 48	0 43
2488	2700	2576	5328	16 6	9.2	104 1	114.3	12	14	59	48	–	–
1800	2490	2980	5100	10 3	8.8	131.5	184.8	12	10	58	56	0 74	0 68
2296	2676	2541	4092	17 0	17 7	61.2	170.5	11	10	41	56	–	–
2218	2059	3283	5412	13.5	7 7	101.9	155.8	13	16	50	59	0 44	0 69
2917	3328	3457	5200	17.8	13 6	115 1	146.5	14	12	59	69	–	–
2332	2584	3938	5814	11 7	8 7	1.0 9	144.8	13	14	49	49	0.5	0.80
1344	2852	2304	5084	11.2	11 1	74.2	107.8	12	18	38	45	–	–
20 4	1952	3610	5348	9 1	5 4	113 6	166 1	14	13	45	51	0.50	0 64
2220	2160	3520	5400	9.5	6 5	154.8	214.5	13	18	71	74	–	–
3058	1794	3463	6348	14 7	5 0	13 4	174 4	13	13	63	56	0 67	0.57
1646	2296	2992	5 00	9.3	7.9	78 5	110.2	16	13	46	46	–	–
2080	1950	3400	6000	9.8	5 4	170.2	165 0	12	13	53	53	0.53	0.54
1970	2480	2600	4464	12.3	9 6	79.8	95 0	11	12	51	48	–	–
2416.9	2201	3417 6	5829	12.8	6.9	125.3	1 04	12 4	14.3	53 7	55.3	0.56	0 68
± 392 1	± 256 8	± 765 1	± 559 1	± 2.8	± 1.5	± 18 1	± 24 0	± 1 7	± 2.5	± 7 1	± 8 6	± 0 09	± 0 14
2235 0	2669	2814 4	4 9 8	4 7	10.8	89 3	127 6	12 7	14.5	49 7	54.8	–	–
± 471 1	± 349.9	± 406.2	± 505 0	± 4.0	± 2.5	± 29.5	± 33 7	± 1 6	± 3 1	± 10 8	± 9.9	–	–

Exercise hemodynamics before and after aortic valvotomy In ten of the 18 patients rest and exercise hemodynamic studies were performed both before and after aortic valvotomy The data on these patients are summarized in Table II

The heart rate and oxygen consumption increase significantly from rest to exercise both pre and postoperatively ($p < 0\ 01$) The levels of heart rate and oxygen consumption obtained preoperatively were not significantly different from the postoperative values suggesting that the level of exercise was similar Each patient preoperatively and postoperatively showed an increase in cardiac index The relationship between exercise cardiac index and the corresponding oxygen consumption was normal in all except one patient (Fig 4) *

The postoperative left ventricular aortic mean pressure gradient measured during exercise (24 7 ± 21 mm Hg) decreased significantly from the preoperative value during exercise (73 4 ± 20 9 mm Hg) (Fig 5*a*) A significant reduction ($p < 0\ 01$) also occurred in the postoperative peak left ventricular systolic pressure during exercise from the preoperative exercise value of 230 ± 19 4 mm Hg to the postoperative exercise value of 176 ± 20 mm Hg (Fig 5*b*) The postoperative increase in the left ventricular systolic pressure that occurred with exercise was *significantly less after surgery than before*

During exercise the DPTI × O /SPTI ratio decreased significantly from resting values both before and after operation ($p < 0\ 01$) Prior to operation the DPTI × O /SPTI ratio decreased from a mean value of 12 8 ± 2 8 at rest to a value of 6 9 ± 1 5 with exercise Each of the ten patients had exercise ratios below 10 before surgery in five patients the value was below 6 5 After surgery although the DPTI × O /SPTI ratio still decreased with exercise the mean value during exercise (10 8 ± 2 5) was significantly higher than before surgery (Fig 6) Postoperatively only four of ten patients had ratios of less than 10 during exercise and no patient had a value of

Table II Exercise hemodynamics

		HR beats/min		*VO* c c /min /M²		*CI* L /min /M		*Mean LV Ao gradient*		*LVPSP* mm Hg	
		R	*E*	*R*	*E*	*R*	*E*	*R*	*E*	*R*	*E*
1	Pre	70	120	151	677	4.3	6 6	60	60	190	220
	Post	80	140	146	933	2 9	8 0	11	15	115	160
2	Pre	70	130	192	710	3 9	9.2	57	81	180	240
	Post	68	120	166	706	3.2	5 9	13	43	135	185
3	Pre	80	150	171	876	4.8	9 6	52	51	170	210
	Post	96	150	146	818	4 7	8 4	19	22	140	180
4	Pre	84	180	160	872	3 6	6.9	59	112	175	240
	Post	80	180	166	1034	4 7	8 6	15	42	135	180
5	Pre	72	150	169	762	4 2	8 4	34	64	170	240
	Post	70	120	167	710	2.9	6 7	0	0	115	160
6	Pre	72	132	163	768	3 6	7 8	53	59	155	200
	Post	66	130	204	783	3.9	9 0	10	0	150	160
7	Pre	110	170	173	785	5 4	8.3	45	55	185	220
	Post	120	155	211	710	4 6	7 0	0	0	148	185
8	Pre	96	150	148	505	4.3	7 7	62	62	190	240
	Post	100	140	212	602	7 1	10 4	47	60	165	220
9	Pre	78	138	164	623	4.9	7 7	46	95	165	230
	Post	80	132	154	685	3 7	6 1	25	37	135	180
10	Pre	100	150	193	768	5.3	8 0	53	95	170	230
	Post	100	155	152	622	5 1	7 4	21	28	120	150
Pre	Mean		147	169	734 6	–	8 0	52 1	73 4	175	230
	STDDev		± 18	± 14.9	112.3	–	± 0.9	± 8.5	± 20 9	± 11.3	± 19 4
Post	Mean		142	172 4	760	–	7.8	16 1	24 7	135	176
	STDDev		± 18 4	± 26.5	± 136	–	± 1 4	± 13 6	± 21 0	± 16 1	± 20 0

HR = heart rate VO = oxygen uptake c c /min M CI = cardiac index LV Ao = left ventricul r aortic LVPSP = l ft ventricular systolic pressure DPTI = diastolic p essure tim interval SPTI = systoli pressure time interval O = arterial o ygen content vols. % SWI = stroke work index LVEDP = left entricula end-diastolic pressure SI = stroke index AVA = aortic valve area

6 the degree of incompetence was assessed as 1+ in six patients 2+ in six patients and 3+ in four patients Two of the four patients with large regurgitant flows had a unicommissural valve at surgery the other two patients had bicuspid valves

DPTI × O /SPTI was calculated to assess indirectly the subendocardial blood flow Of the 18 patients the preoperative resting DPTI × O /SPTI ratio was less than 10 in eight patients and greater than 10 in the other ten patients For the entire group of patients flow ratio at rest correlated inversely with the mean gradient (r = –0 5) LV pressure (r = –0 56) and heart rate (r = –0 72) The flow ratio did not correlate well with the aortic valve area (r = 0 17) Following operation only four patients had a DPTI × O /SPTI of less than 10 In three of these patients (Cases 8 16 and 17) the reduced ratio reflected residual obstruction since in each patient the resting left ventricular aortic mean pressure gradient was 40 mm Hg or more after surgery In the fourth patient (Case 9) although the mean gradient was reduced there was a marked increase in the severity of aortic insufficiency For the entire group postoperatively there was a significant increase in the DPTI × O /SPTI from a preoperative mean value of 11 1 ± 3 3 to a postoperative mean value of 13 5 ± 3 8 ($p < 0\ 01$) (Fig 3) The increase in this ratio is related mainly to the reduction in systolic pressure time interval from a preoperative mean value of 3 839 9 ± 773 to a postoperative mean value of 3 048 ± 521 4 mm Hg sec / min There was little change in the DPTI following surgery decreasing from 2 338 2 ± 382 mm Hg sec /min to 2 269 7 ± 497 3 mm Hg sec / min A slight decrease in DPTI may be related to the increased degree of aortic insufficiency and lowering of aortic diastolic pressure

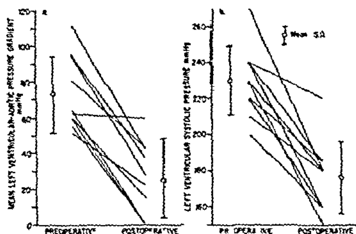


Fig 5 Pre and postoperative mean left ventricular aortic pressure gradient (a) and left ventricular systolic pressure (b) on exercise

exercise in spite of an increase of the LVEDP is abnormal and indicates persistent cardiac dys function

Discussion

Aortic valvotomy is the recognized treatment for children with severe valvar aortic stenosis which is usually defined hemodynamically as an aortic valve area of less than 0 5 0 7 cm /M or a peak systolic left ventricular aortic pressure gradient greater than 70 mm Hg[?] Ideally aortic valvotomy in children should be a low risk procedure should remove the known risk of sudden death prevent the myocardial dysfunction seen in adults and restore normal rest and exercise hemodynamics

The operative mortality rate of aortic valvotomy is very low successful surgery significantly reduces the risk of sudden death Although most of the patients show a significant reduction in the resting left ventricular aortic pressure gradient some have major residual stenosis and many have a major increase in aortic insufficiency Of our 18 patients three had moderate or severe residual stenosis following valvotomy while another four had a major degree of postoperative aortic insufficiency Although this is a selected group of patients others have reported similar results Thus Bernhard and associates reported similar results in a large series of patients after aortic valvotomy It is likely that the residual problems are related more to the pathologic anatomy of the aortic valve than to inadequate surgical technique In patients with unicommissural valves inadequate relief of stenosis or the development of severe valvular insufficiency may be inevitable

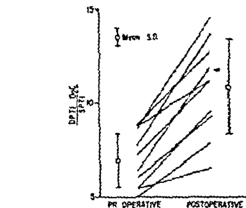


Fig 6 Pre and postoperative DPTI × O /SPTI on exercise DPTI = diastolic pressure time interval (mm Hg sec / min) SPTI = systolic pressure time interval (mm Hg sec / min) O = arterial oxygen content vols %

The preoperative exercise hemodynamics in our study are similar to those which we have previously reported in a large series of children with aortic stenosis The left ventricular systolic pressure and mean left ventricular aortic pressure gradient increased on exercise in all patients The increase in pressure gradient was less than expected for the concomitant increase in cardiac output so that calculated aortic valve area increased on exercise in comparison to the resting value This observation has previously been documented by Bache and associates and is due either to an alteration in valve configuration with an actual increase in valve area on exercise or to a computational artifact

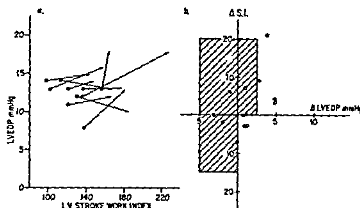


Fig 7 a Change in preoperative left ventricular end-diastolic pressure (*LVEDP*) relative to change in left ventricular (*LV*) stroke work index on exercise The direction of change is indicated *by the arrow b* Preoperative (*closed circle*) and postoperative (*open circle*) change in left ventricular stroke index (*SI*) on exercise relative to change in LVEDP *The shaded area* represents the normal response

The increase in cardiac output produced by supine leg exercise was mainly the result of an increase in heart rate The stroke volume changed little In some patients there was a decrease in stroke index in spite of an increase in LVEDP suggesting decreased myocardial function If the change in stroke work index on exercise is compared to the change in LVEDP on exercise then all the children showed a normal response with a major increase of stroke work index associated with only a slight increase or no change in the LVEDP This is in sharp contrast to exercise studies done in adults with severe aortic stenosis where many patients showed an actual decrease or little change in SWI in spite of a major increase in LVEDP on exercise and suggests more severe myocardial dysfunction in adults with aortic stenosis There were several possible explanations for this

1 Aortic stenosis becomes increasingly severe with age particularly with calcification of the aortic valve in older adults

2 Long-standing myocardial hypertrophy results in increased myocardial dysfunction

3 Myocardial ischemia related to decreased coronary perfusion in the face of increased demand and complicated by coronary atherosclerosis

Probably all three factors contribute to increasing myocardial dysfunction with age

The postoperative exercise studies in our patients show a significant improvement compared to the preoperative exercise hemodynamics The peak left ventricular pressure and mean left ventricular aortic pressure gradient on exercise are significantly decreased by successful surgery Some patients in this study still showed a decrease in stroke volume on exercise in spite of an increasing LVEDP In most this may be artifact since they had aortic insufficiency and the Fick stroke volume underestimates the true forward stroke volume In one patient however there was no aortic insufficiency and so this explanation does not apply and he clearly still has evidence for ventricular dysfunction. In previous pre and postoperative rest and exercise hemodynamic studies in patients with pulmonary stenosis who had a pulmonary valvotomy all the postoperative patients showed a normal relationship between the stroke index and RVEDP on exercise in contrast to a high percentage which had shown an abnormal response before surgery Pulmonary valvotomy is more effective in reducing right ventricular systolic pressure and right ventricular pulmonary artery pressure gradient at both rest and exercise and resulted in a significant decrease in the right ventricular end diastolic pressure at rest and exercise after surgery This probably reflects a reduction in the degree of right ventricular hypertrophy and reflects better results from pulmonary valvotomy Also pulmonary insufficiency is relatively unimportant and this permits the surgeon to be more vigorous in his attempts to open the valve accounting for the better result

The role of aortic stenosis in producing subendocardial ischemia in children and adults has received considerable attention recently The papillary muscle infarction seen in some young infants with severe congenital aortic stenosis represents an extreme example of subendocardial ischemia The ST segment depres

sion which may be present at rest or can be produced by exercise in some children with moderately severe or severe aortic stenosis probably reflects the myocardial ischemia induced by an increased work load

The DPTI × O /SPTI ratio has been shown experimentally to correlate with other methods of estimating subendocardial blood flow A ratio of less than 10 was regarded by Lewis and associates as indicating subendocardial ischemia and was common in their patients who had severe valvar aortic stenosis (aortic valve area less than 0 7 cm /M) Forty four % of our patients had a resting value of less than 10 prior to operation and all patients exercised had a ratio of less than 10 Buckberg and colleagues detected evidence of abnormal lactate metabolism when the DPTI TTI (Tension Time Index) ratio was less than 0 3 This approximates to a DPTI × O / SPTI of 6 or less Only one of our patients had a ratio of less than 6 at rest preoperatively This patient was three months old and had a calculated aortic valve area of less than 0 36 cm /M and a heart rate of greater than 180 The combination of severe aortic stenosis with a low aortic valve area and a high heart rate results in a low ratio Twelve of 80 patients studied by Lewis and co workers had ratios less than 6 all had an aortic valve area of less than 0 45 cm /M or heart rates above 120 Eight of the 12 were less than one year of age Subendocardial ischemia is therefore a greater problem in infants with severe stenosis and contributes to the poor prognosis in patients with severe aortic stenosis in infancy

Exercise results in an increase in the systolic pressure and heart rate and a decrease in diastolic filling time Thus it is not surprising that each of our patients with severe aortic stenosis showed a major decrease in DPTI × O /SPTI with exercise in all patients the ratio dropped to less than 10 and in three patients to less than 6 Successful aortic valvotomy resulted in a significant improvement in this ratio both at rest and on exercise reflecting improved myocardial perfusion

The postoperative rest and exercise hemodynamics including the indirect assessment of subendocardial ischemia using the DPTI × O / SPTI ratio are not only useful in assessing the results of surgery but also in determining the advisability of normal exercise activity after valvotomy Those patients with only minor residual gradients or minimal aortic insufficiency normal exercise response and normal DPTI × O /SPTI ratios at rest and exercise can probably be permitted normal exercise activity Restrictions placed on other patients would depend upon the degree of residual abnormalities at rest and exercise

Summary

The rest and exercise hemodynamics in children with congenital valvar aortic stenosis were studied before and after aortic valvotomy Eighteen patients were studied at rest ten of the 18 patients were also studied during supine leg exercise using a bicycle ergometer

Aortic valvotomy resulted in a significant reduction in the mean left ventricular aortic pressure gradient and in peak left ventricular systolic pressure with an increase in aortic valve area in most patients There was an associated increase in the subendocardial blood flow assessed indirectly by the DPTI × O /SPTI ratio There was a minor increase in the degree of aortic insufficiency in most patients

Although in general there was significant hemodynamic improvement three of the 18 patients still had significant residual stenosis after surgery and another four patients had a major increase in aortic insufficiency The three patients with residual obstruction and one of the four patients with moderate to severe aortic insufficiency still had a DPTI × O /SPTI ratio of less than 10 suggesting possible residual subendocardial ischemia Also the increased left ventricular end-diastolic pressures (LVEDP) present in nearly 50% of the patients before surgery did not change significantly after surgery Three patients showed an actual increase in LVEDP after surgery

Before surgery the left ventricular systolic pressure and mean gradient increased on exercise but this increase was proportionately less than the increase in cardiac output so that calculated aortic valve area increased on exercise The DPTI × O /SPTI ratio decreased significantly on exercise suggesting an increase in myocardial ischemia Successful surgery resulted in a reduction in left ventricular systolic pressure and mean left ventricular aortic gradient on exercise and in improvement in the subendocardial blood flow as assessed by the DPTI × O /SPTI ratio

In general children with severe aortic stenosis have relatively normal cardiac function
cise Some children did show a reductio

index on exercise in spite of rising LVEDP However stroke work index increased in all of our children Adult studies have shown many patients with decrease in stroke work index relative to LVEDP on exercise

The results of pre and postoperative rest and exercise hemodynamics may be useful in evaluating results of surgery the postoperative hemodynamic evaluation including the use of DPTI × O /SPTI ratio provides additional useful information which can be used in making decisions concerning exercise activity after surgery

REFERENCES

1. Nadas, A S and Fyler D C Pediatric Cardiology Philadelphia 1972, W B Saunders Company
2. Rudolph A M Congenital Diseases of the Heart Chicago 19 4 Year Book Medical Publishers Inc pg 327
3. Moss A J Adams F H and Emmanoulides G C Heart Disease in Infants Children and Adolescents Baltimore 19" The Williams & Wilkins Company pg 111
4. Anderson F L Tsagaris T J Tikoff G Thorne J L Schmidt A M and Kuida H Hemodynamic effects of exercise in patients with aortic stenosis Am J Med 46 872, 1969
5. Gorlin R and Gorlin S G Hydraulic formula for calculation of the area of the stenotic mitral valve other cardiac valves and central circulatory hunts Am Heart J 41 1 1951
6. Lewis A B Heyman M A Stanger P Hoffman J I E and Rudolph A M Evaluation of subendocardial ischemia in valvar a rti stenosis in children Circulation 49 9 8 1974
7. Hoffman J I E and Buckberg G D The myocardial supply demand ratio—a ritical review Am J Cardiol 41 32 19 8
8. Frank M J Casanegra P Nadimi M Mighon A J and Levinson G E Mea urement of aortic regurgitation by upstream sampling with continuous infusion of indicator Circulation 33 545 1966
9. Barratt Boyes B G and Wood E H Cardiac output and related measurements and pressure values in the right heart and associated vessels together with an analy is of the hemodynamic response to the inhalation of hi h oxygen mixtures in healthy subjects, J Lab Clin Med 51 " 1958
10. Donald K W Bishop J M Cumming G and Wade O L The effect of exercise on the cardiac output and circulatory dynamics of normal subjects Clin Sci 14 37 1955
11. Ross J Gault J H Mason D T Linhart J W and Braunwald E Left ventricular performance during muscular exercise in patients with and without cardiac dysfunction Circulation 34 597 1966
12. Conkle D M Jones M and Morrow A G Treatment of congenital aortic stenosis Arch Dis Surg 107 649 1973
13. Lawson R M Bonchek L I Menashe V and Starr A Late results of surgery for left ventricular outflow tract obstruction in children J Thorac Cardiovasc Surg 71 334 1976
14. Bernhard W F Keane J F Fellows K E Litwin S. B and Gross R E Progress and problems in the surgical management of congenital aortic stenosis J Thorac. Cardiovasc Surg 66 404 1973
15. Cueto L and Moller J H Haemodynamics of exercise in children with isolated aortic valvular disease Br Heart J 35 93 1973
16. Bache R J Wang Y., and Jorgensen C R Hemodynamic effects of exercise in isolated valvular aortic stenosis, Circulation 34 1003 1971
17. Mody M R and Mody G T Serial hemodynamic observations in congenital valvular and subvalvular aortic stenosis Am Heart J 89 137 19 5
18. Hurst J W Logue R B Schlant R C and Wenger N K The Heart New York 1978 McGraw Hill Book Company Inc pg 1033
19. Braunwald E Ross J and Sonnenblick, E H Mechanisms of Contraction of the Normal and Failing Heart. Boston 1976 Little Brown & Company pg 319
20. Buckberg G Eber L Herman M and Gorlin R Ischemia in aortic stenosis Hemodynamic prediction Am J Cardiol. 35 "78 1975
21. Stone F M Bessinger F B Lucas, R V and Moller J H Pre and postoperative rest and exercise hemodynamics in children with pulmonary stenosis, Circulation 49 1102, 1974
22. Vincent W R Buckberg G D and Hoffman J I E Left ventricular subendocardial ischemia in severe valvar and supravalvar aortic stenosi Circulation 49 3 6, 1974
23. Lakier J B Lewis A B Heymann M A Stanger M D Hoffman J I E and Rudolph A M Isolated aortic stenosis in the neonate Natural history and hemodynamic considerations, Circulation 50 801 1974
24. Moller J H Nakib A and Edwards J E Infarction of the papillary muscle and mitral insufficiency associated with congenital aortic stenosis Circulation 34 87 1966
25. Halloran K H The telemetered exercise electrocardiogram in congenital aortic stenosis Pediatrics 47 31 1971
26. Chandramouli, B Ehmke D A and Lauer R M Exercise induced electrocardiographic changes in children with congenital aortic stenosis J Pediatr 87 ~ 1975
27. Brazier J., Cooper N and Buckberg G The adequacy of subendocardial oxygen delivery Circulation 49 968, 1974

Exercise-induced ventricular ectopy in children and young adults with complete heart block

Robin B Winkler M M S M D
Michael D Freed M D
Alexander S Nadas M D
Boston Mass

The response of patients with non ischemic complete heart block (CHB) to exercise has long been of interest to cardiologists Most investigators have focused on the heart rate response and on the compensatory changes that enable these patients to maintain a cardiac output appropriate to their activity despite the often profound bradycardia Some have noted the appearance of ventricular ectopic activity (VEA) during strenuous exercise even in the absence of associated structural heart disease The purpose of this study was to investigate the frequency and severity of exercise elicited ventricular ectopy in young people with non ischemic heart block and to attempt to interpret its clinical significance

Subjects and methods

CHB subjects The study group (Table I) consisted of 25 children and young adults aged 3 to 29 years (median age 17 years) with complete atrioventricular block Patients who were acutely ill those with transient block or cardiac pacemakers and those receiving cardiac medications were excluded from this study There were 17 males and eight females Fourteen of the patients had isolated or congenital block with no associated structural defects and no history of illness predisposing to aquired block Seven patients with block had associated cardiac defects six of these had L-transposition of the great arteries complexes (L-TGA) (congenitally corrected transposition) Four patients had surgically acquired block following repair of assorted congenital defects

Control subjects The control group was made up of 50 children and young adults without heart disease who were referred for exercise testing for evaluation of atypical chest pain poor exercise tolerance hypertension or syncope None of these patients had significant heart disease on the basis of physical examination electrocardiogram (ECG) and in most cases chest x ray Those who were referred for evaluation for possible arrhythmia (e g history of palpitations conduction abnormalities on resting ECG) were excluded as were those receiving cardiac medication

Procedure Each subject underwent a graded maximal exercise test on the treadmill with the speed and grade of the treadmill increased every three minutes according to the Bruce protocol Leads II aV_F and a modified V_5 were monitored continuously starting three minutes prior to exercise and extending through ten minutes of recovery and were recorded photographically on a Sanborn Polybeam recorder with simultaneous magnetic tape recording system for playback where desired Exercise was terminated when the subject reached the limit of his or her tolerance Only those who exercised past their anerobic threshold verified by venous serum lactate levels of 6 0 mEq /L or greater at one minute of recovery were included

Analysis of data All exercise test tracings were reviewed for presence degree and frequency of

From th Department of Cardiol gy The Chil ren s Hospital Medical Cent r and the D partment of Pediatrics Harvard Medical School, Boston Mass

Supported in part by G ants T10 5855-0 and P01 HL 10436-08 fr m the Nat onal Heart Lung and Blood Inst tute

Rec ed f r publ cati n Sept 29 19 8

Accepted fo publication Feb 2 1979

Reprint requests Micha l D Freed M D Dept of Cardiology Children Hosp tal Med cal C nte 300 Longwood A Boston Mass 0 115

000?-8 03/80/010087 + 06500 60/0 © 1980 The C V Mosby Co

Table I Summary of data on 25 patients with complete heart block

	Case No	Sex	Age (yrs)	Defects	QRS duration (sec)	Heart rate		Endurance time Bruce protocol (min)	Exercise tolerance (%ile)	Ectopy score	
						Rest	Exercise			Rest	Exercise
Group 1											
Congenital	1	F	17	None	0.04	54	120	10.5	50	1	3
	2	M	24	None	0.08	52	105	11.5	10	0	4
	3	F	19	None	0.06	39	105	12.8	>90	0	4
	4	M	17	None	0.08	55	146	13.5	50	0	3
	5	M	24	None	0.12	43	76	13.2	50	0	5
	6	M	7	None	0.08	48	95	12.0	50	0	0
	7	M	24	None	0.09	44	70	9.5	<5	0	3
	8	F	21	None	0.08	43	82	9.1	25	0	0
	9	M	16	None	0.08	50	100	17.3	>90	0	0
	10	F	14	None	0.04	60	126	11.3	50	0	2
	11	F	13	None	0.11	46	109	12.4	50	0	3
	12	M	4	None	0.12	47	51	6.7	10	0	0
	13	F	13	None	0.08	50	103	13.7	75	0	2
	14	F	21	None	0.07	36	105	9.8	25	0	3
Group 2											
Associated defects	15	M	14	L-TGA	0.11	80	129	13.3	25	2	4
	16	M	20	MR	0.06	42	120	16.3	>90	0	2
	17	M	5	L-TGA	0.10	57	68	6.8	10	0	0
	18 †	M	25	L-TGA	0.14	53	68	6.5	<5	1	5
	19	M	29	L-TGA	0.10	63	96	8.5	<5	1	5
	20	M	24	L-TGA	0.07	73	90	5.6	<5	0	0
	21 †	M	27	L-TGA	0.16	63	97	7.0	<5	0	4
Group 3											
Surgical	22	F	23	TOF	0.14	38	62	7.2	<5	0	5
	23	M	10	D-TGA	0.08	47	118	13.8	75	0	0
	24 †	M	21	ASD 1 MR	0.14	73	170	8.3	<5	3	5
	25	M	15	TAPVR	0.06	63	81	11.4	10	0	0

§ Subsequently received pacemakers.
† Died.
See Table II
Abbreviations TGA = transposition of the great arteries MR = mitral regurgitation TOF = tetralogy of Fallot ASD 1 = atrial septal defect, primum TAPVR = total anomalous pulmonary venous return.

ventricular ectopy grading the ectopic activity by a modification of the system suggested by Lown and Wolf (Table II) Each subject was assigned a resting score and exercise score The former was the highest grade of ectopy seen on either the routine ECGs for the year preceding the test or during the control period before the exercise test The latter was the highest grade of ectopy seen during exercise or early in the recovery period Exercise tolerance expressed in percentile for age and sex is derived from a comparison of duration of maximal exercise with data from normal untrained subjects

The Kolmogorov Smirnoff test for the deviation between two sample cumulatives was used for analysis of the severity of ectopy (according to the Lown and Wolf criteria) and the chi square test was employed for analysis of its frequency Linear regression was used to evaluate the relationship between heart rate and both age and severity of ectopy

Results

Background data and the results of exercise testing are summarized in Table I Grade 1 ectopy occurred at rest in three of 25 (12%) CHB subjects

Table II Grading of ventricular ectopy

0	No ectopy	
1	Unifocal PVC	<1/minute
2	Unifocal PVC	>1/minute
3	Multifocal PVC	
4	Couplets (paired PVC)	
5	Ventricular tachycardia	

Abbreviations PVC = premature ventricular contractions

and none out of 50 of the controls (p > 0 05) No Grade 1 ectopy was induced by exercise in either group The frequency of significant ectopy (Grade 2 or higher) at rest and at exercise in the subjects with heart block and the controls is illustrated in Fig 1 At rest there was no significant difference with regard to the frequency of significant ectopy none out of 50 in the control group and two of 25 (8%) in the heart block group (p = >0 10) At exercise however significant ectopy was present in 68% (17 of 25) of patients with heart block but only 2% (one of 50) of the controls (a girl with a single couplet) (p = <0 01) Of the 17 patients with heart block who developed ectopy complex forms (Grade 3 4 or 5) were present in 82% (14 of 17) The heart block patients showed a significantly higher grade of ventricular ectopy than the controls (p = <0 01) The three groups those with isolated congenital block those with block and associated lesions and those with surgically induced heart block did not differ significantly either in frequency or severity of ventricular ectopy on exercise (p = >0 10) The appearance of ventricular ectopy was age related no ectopy was induced in children under ten years of age and the most advanced forms were induced in the patients over 20 years of age (Fig 2) This trend toward increasing frequency and severity of ventricular ectopic activity with age is significant at the 0 05 level

There was no appreciable correlation between age and resting ventricular rate (r = 04) or between age and maximum ventricular rate achieved with exercise (r = 03) nor was resting heart rate correlated with ventricular ectopy on exercise (r = 06) The proportion of patients with ectopy increased with increasing maximum heart rate but not significantly (p = 0 16) and the scatter of the data was such that they were consistent also with a weak trend in the opposite direction that is for increasing ectopy with decreasing maximum rate

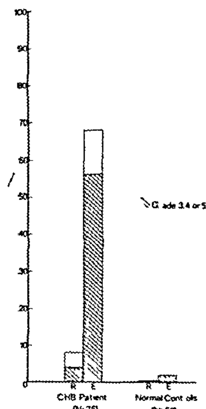


Fig 1 Frequency of significant ventricular ectopy (Grade 2 or higher) at rest (*R*) and with exercise (*E*) in 25 patients with complete heart block (*CHB*) and in 50 control subjects

Patients with QRS duration greater than two standard deviations above the mean for age[1] on the resting electrocardiogram were compared with the remainder of the heart block patients (Fig 3) Those with prolongation showed a greater frequency of very severe (Grade 3 4 or 5) ectopy with exercise (p = <0 05) than did those with a normal QRS duration

No significant difference was seen between the girls and the boys in either frequency or severity of ectopy induced

Exercise tolerance was diminished (greater than two standard deviations below the mean for age and sex) in seven of 25 (28%) of the patients with heart block (one of 14 (8%) with congenital block four of seven (57%) with associated lesions and two of four (50%) with surgically induced block) Normal tolerance occurred significantly more frequently in the congenital CHB patients than in the remainder of the subjects (p = <0 01) The subjects with diminished tolerance did not differ significantly from those with normal tolerance in either frequency (p = >0 10)

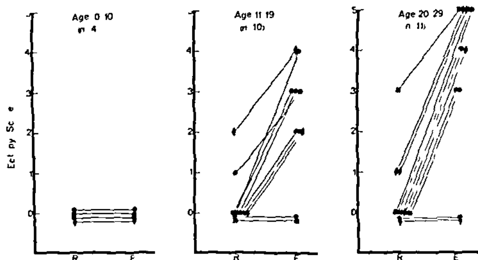


Fig 2 Age distribution of ventricular ectopy at rest (*R*) and with exercise (*E*) in 25 patients with complete heart block. Symbols ● congenital block ⸸ associated cardiac defects ■ surgical block.

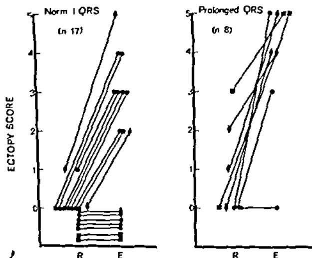


Fig 3 Ventricular ectopy score at rest (*R*) and with exercise (*E*) in 17 CHB patients with normal QRS duration and in eight patients with prolonged QRS Symbols same as in *Fig 2*

or severity ($p = >0.05$) of ventricular ectopy at rest or with exercise no significant difference in age ($p = >0.10$) or QRS duration ($p = >0.10$) was found between these two groups

Clinical follow up of the patients for up to 36 months since exercise study reveals 19 who are asymptomatic on no cardiac medications The remaining six have undergone implantation of permanent demand mode pacemakers two for Adams Stokes attacks and two for maintenance of ventricular rate during pharmacological suppression of ventricular ectopy and in two concurrently with intracardiac repair or complex congenital heart disease Four of these patients were placed on antiarrhythmic medications

There have been three sudden deaths (Case No 18 21 and 24) These patients were over 2 years of age had associated cardiac disease an had shown Grade 4 or 5 ventricular ectopi activity on exercise All three had high grad ventricular ectopy at rest after the placement o functioning pacemakers and the administratio of antiarrhythmic agents Repeat exercise testin after pacemaker insertion had not been per formed

Discussion

We found ventricular ectopy to occur frequent ly with exercise in children and young adults wit complete heart block Although this phenomeno has been noted previously it has not been system atically examined in a sizable series Of th reported cases of children with heart block i whom the presence or absence of ventricula ectopy on exercise is mentioned it was elicited i 39% (24 of 61)[1,4] Our incidence was somewha higher possibly because our protocol require maximal exercise which has been shown to b more sensitive in elicitation of ventricular ectop than submaximal exercise [3]

The prognostic significance of ventricular ecto py is not clear Several studies in normal adult and in adults with coronary heart disease hav shown a higher risk of sudden death in those wit ectopy especially with high grades of ectopy Children with isolated congenital block are als at risk for sudden death Although such death were originally attributed to bradycardia [11] chi

dren like their adult counterparts[18, 19] may have Adams Stokes attacks in some cases fatal due to ventricular tachycardia or fibrillation[9] The presence of severe ectopy at rest or at exercise may help to identify the child at risk An artificial pacemaker may not completely protect the heart block patient from this type of Adams Stokes attack as was unfortunately demonstrated in three of our patients

No difference was found in our study in the incidence or severity of ectopy between those patients with isolated congenital block those with surgical block and those with associated structural defects This was somewhat unexpected in light of the reported association of surgically acquired block with a high risk of sudden death[1] contrasted to the more benign prognosis[7] of isolated congenital block Our sample of patients with surgical block is a small one however and biased toward the most stable since the large majority of children with surgically acquired heart block in our institution receive pacemakers early and hence were not eligible for this study No deaths have as yet occurred among the 14 isolated heart block patients including those with high grade ectopy on exercise suggesting that the over all risk for sudden death in CHB may be higher in those with associated heart disease reflecting other factors such as congestive failure or hypoxemia in addition to the presence and severity of ectopy

Ventricular ectopy was more likely to occur and was more severe among older patients independent of QRS duration Although longitudinal data on ectopy in patients with complete heart block are not yet available this age relationship raises the possibility that heart block even in its isolated congenital form may be a progressive disease The tendency to more severe forms of ectopy in subjects with QRS prolongation is not unexpected such patients are known to be at increased risk of syncope and sudden death

In fact in the first description of Adams Stokes attacks in children with congenital complete heart block reported by Molthan and associates in 1962 QRS prolongation was present in the two documented cases in which ventricular ectopy initiated the attacks A more detailed analysis of the contribution of the level of block would require electrophysiologic studies which were not available in a majority of our subjects

Exercise tolerance was normal in our patients with isolated congenital heart block but was significantly limited in some with associated heart defects or surgically acquired block as has been shown by other investigators[3] Ventricular ectopy was not related to tolerance and many patients developed the worst arrhythmias during the recovery period supporting the concept that ectopy occurs in response to stress relative to the individual rather than to the predicted norm

The etiology of ectopy in complete A V block remains unknown That it occurs purely as a reflection of low ventricular rate is unlikely in light of the low incidence of ectopy at rest The absence of a significant trend toward increased ectopy on exercise with lower heart rates is in agreement with the data of Ikkos and Hanson[3] We were unable to substantiate the assertion of Chawla and co workers that the elicitation of ventricular ectopic activity was associated with inadequate chronotropic effect Our data support the premise of Levy and colleagues[1] that CHB is a complex disease rather than a simple problem of low heart rate However the small number of patients previously reported[4] and those added here is insufficient to answer this question definitively

We have demonstrated a tendency toward ventricular ectopy on exercise in children and young adults with complete heart block We believe that there may be an increased risk for sudden death in those patients with ectopy especially in the older patients with associated cardiac abnormalities and that pacemakers may not necessarily be protective

Summary

Twenty five children and young adults with complete heart block and 50 normal control subjects were maximally exercised on a treadmill and their electrocardiograms were analyzed for the presence and degree of ventricular ectopy activity Sixty eight % (17 of 25) of the heart block patients had significant ventricular ectopy (frequent unifocal ectopy or worse) on exercise compared to 2% (one of 50) of the controls ($p = < 0.01$) In the patients with block there was a significant trend toward more frequent and more severe ectopy with increasing age ($p = < 0.05$) independent of heart rate

More severe ventricular ectopy was also seen in those patients with QRS prolongation ($p = < 0.05$) No significant differences were

found between the 14 patients with isolated congenital heart block the seven with associated defects and the four with surgically acquired block We believe that severe ventricular ectopy is common at exercise in patients with complete heart block and they may have an increased risk for sudden death

We would like to thank Drs Olli Miettinen and R Curtis Ellison for their guidance Dr Thomas Graboys for assistance in reviewing the tracings and Mrs Pat Faulkner and Mrs Ilene Burton for their help in the preparation of the manuscript

REFERENCES

1 Zander E Zur Frage von der Wirkung der extrakardialen Nerven auf den automatisch schlagenden Ventrikel Nord Med Ark 48 Abt 11 No 6 1915
2 Holmgren A Karlberg P and Pernow B Circulatory adaptation at rest and during muscular work in patients with complete heart block Acta Med Scand 164 119 1959
3 Ikkos D and Hanson J S Response to exercise in congenital complete atrioventricular block Circulation 22 583 1960
4 Taylor M R H and Godfrey S Exercise studies in congenital heart block Br Heart J 34 930 1972
5 Kramer J D and Lurie P R Maximal exercise tests in children Am J Dis Child 108 283 1964
6 Miller R A., and Rodriquez Coronel A Congenital atrioventricular block *in* Moss A J and Adam F H eds Heart Disease in Infants Children and Adolescents, Baltimore 1968 The Williams & Wilkins Company p 1039
7 Thoren C Herin P and Vavra J Studies of ubmaximal and maximal exercise in congenital complete heart block, Acta Paediatr Belg 28(Suppl) 13? 19?4
8 Chawla K Serratto M Cruz J Chuquimia R Miller R., Hastreiter A and Towne W D Response to maximal and submaximal exercise testing in patients with congenital complete heart block Circulation 55 and 56(Suppl III) 171 197?
9 Doan A E Peterson D R Blackmon J R and Bruce R. A. Myocardial ischemia after maximal exercise in healthy men Am Heart J 69 11 1965
10 Lown B and Wolf M Approaches to sudden death from coronary artery disease Circulation 44 130 19 1
11 Cumming G R Everatt D and Hastman L Bruce treadmill test in children normal values in a clinic population Am J Cardiol 41 69 1978
12 Ziegler R F Electrocardiographic studies in normal infants and children Springfield 1951 Charles C Thomas p 129
13 Blackburn H Taylor H L Hamrell B Buskirk E Nicholas W C and Thorsen R D Premature ventricular complexes induced by stress testing Am J Cardiol 31 441 1973
14 Hinkle L E Carver S T and Stevens M The frequency of asymptomatic disturbances of cardiac rhythm and conduction in middle aged men Am J Cardiol 24 629 1969
15 The Coronary Drug Project Research Group Prognostic importance of premature beats following myocardial infarction J.A M.A 223 1116 1973
16 Nakamura F F and Nadas A S Complete heart block in infants and children N Engl J Med. 270 1?61 1964
17 Michaelsson M and Engle M A Congenital complete heart block An international study of the natural history Cardiovasc Clin 4 85 1972
18 Wilson F N., Wishart S W Macleod A G and Barker P A A clinical type of paroxysmal tachycardia of ventricular origin in which paroxysms are induced by exertion Am Heart J 8 155 1932
19 Parkinson J Papp C and Evans W The electrocardiogram of the Stokes Adams attack Br Heart J 3 1?1 1941
20 Molthan M E Miller R A Hastreiter A R and Paul M H Congenital heart block with fatal Adams Stokes attacks in childhood Pediatrics 30 3? 196?
21 Lillehei, C W Sellers R D Bonnabeau R C and Eliot R S Chronic post surgical complete heart block, J Thorac Cardiovasc Surg 46 436 1963
22 Rowe J C and White P D Complete heart block A follow up study Ann Intern Med 49 260 1958
23 Jouve A Gerard R Torresani J and Arnoux M Les blocs auriculoventriculaires congenitaux complets Mal Cardiovasc 7 271 1966
24 Levy A M Camm A J and Keane J F Multiple arrhythmias detected during nocturnal monitoring in patients with congenital complete heart block Circulation 55 247 1977

Case reports

Echocardiographic detection of a retained left atrial catheter

Aung Win M D
John O Pastore M D
Deborah Coletta
Rudolph J Junda M D
Boston Mass

Echocardiography has become an established diagnostic tool in the evaluation of patients who have recently undergone open heart surgery Extensive experience has now been gained with the use of this diagnostic method in the detection of postoperative pericardial effusion[1,2] Echocardiographically demonstrable changes in segmental left ventricular function following coronary or valvular surgery have been described[3] The function of valve prostheses in the early postoperative period has also been studied through this noninvasive means[5]

We have recently used M Mode echocardiography to detect a retained left atrial catheter in a patient with unusual neurologic signs following open heart surgery Documentation of the presence of the catheter within the left atrium led to reoperation and removal of the foreign body

Case report

An 18-year-old woman was admitted with congestive heart failure resulting from penetrating chest trauma. She underwent the surgical repair of mitral and tricuspid valve lacerations and closure of a traumatic interventricular septal defect A left atrial catheter (B D Vinyl Marked Tubing No 6118) was implanted at the time of operation in order to facilitate hemodynamic monitoring in the postoperative period On the fifth postoperative day the left atrial catheter was noted to be non functional and was presumed to be occluded by thrombus An attempt to remove it completely at the bedside was unsuccessful, but it was felt by the surgeon that the line had been withdrawn sufficiently so that the entire catheter was extra-cardiac A routine chest x ray failed to demonstrate the position of the catheter in fact no portion of the catheter could be seen on the chest film.

Five days later the patient developed transient left homonymous hemianopsia which was thought most likely due to a cerebral embolism Anticoagulation therapy was begun An echocardiogram (Fig 1) showed a markedly dense linear echo within the left atrium The diagnosis of intra atrial catheter retention was made and complete removal of the left atrial catheter was performed via thoracotomy under general anesthesia At surgery the proximal end of the catheter was located in the pericardial space held only by an anchoring suture on the lateral pericardium. The catheter was withdrawn from its insertion site in a superior pulmonary vein without difficulty and the left atrium was not re-opened Thrombus filled the distal lumen of the catheter

Subsequently the patient did well without any further embolic episodes. An echocardiogram was repeated (Fig 2) and the dense echo band was no longer present in the left atrium

The patient has been free of symptoms during the 16 months since the removal of the left atrial catheter

Discussion

The presence of catheters within cardiac chambers is usually detectable echocardiographically Since they are foreign bodies of considerable width Swan Ganz catheters reflect ultrasound strongly and have within the heart characteristic motion patterns which have been well described[6,7] During routine cardiac catheterization it is possible to follow the motion pattern of intracardiac catheters as they traverse the chambers on both sides of the heart However there have been no previous reports of the echocardiographic appearance of cardiac catheters in the left atrium either at the time of cardiac catheterization or following cardiac surgery

In our patient the demonstration of a catheter in a left heart chamber had great the

From the Departments of Medicine (Cardiology Division) and Radiology St Elizabeth's Hospital, and Tufts University School of Medicine Boston Mass

Received for publication Sept 22, 1978

Accepted for publication Nov 3 1978

Reprint requests Dr John O Pastore Cardiology Division, St Elizabeth's Hospital, 736 Cambridge St., Boston Mass 02135

0002-8703/80/010093 + 03$00.30/0 © 1980 The C V Mosby Co.

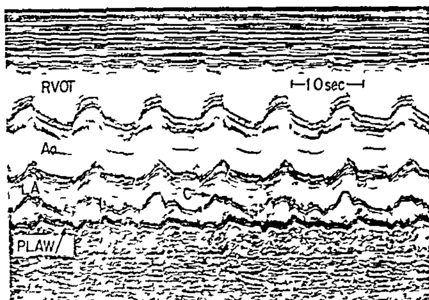


Fig 1 Echocardiogram before the removal of the intra atrial catheter The catheter *(C)* is visualized as a markedly dense linear echo within the left atrium *RVOT* = right ventricular outflow tract *Ao* = aortic root *LA* = left atrium *PLAW* = posterior left atrial wall

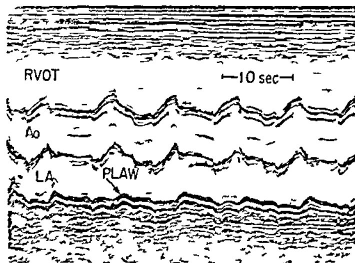


Fig 2 Echocardiogram after the removal of the intra atrial catheter The linear band is no longer seen within the left atrium *RVOT* = right ventricular outflow tract *Ao* = aortic root *LA* = left atrium *PLAW* = posterior left atrial wall

implications The catheter had become non functional several days following surgery In our experience this problem has always been due to occlusion of the line by thrombus and we always advise removal of such lines as soon as the left atrial pressure is damped However in this case normal traction upon the external portion of the catheter failed to dislodge it from the chest completely Nevertheless, the surgeon performing the procedure felt that the catheter had been removed from the heart Examination of the routine chest x ray was not helpful since the catheter could not be located on the film Echo demonstration of the intracavitary position of the catheter was followed promptly by return of the patient to the operating room for complete removal of the device The echo free appearance of the left atrium following this procedure confirmed the impression that the echo dense linear band had been due to the catheter

We have presumed that her neurologic syndrome preceding final removal of the catheter

was due to systemic emobolization from the catheter tip while it was still within the left atrium Inspection of the catheter after its removal from the left atrium did demonstrate extensive fibrin thrombus in its distal lumen The left atrium itself was not re explored since the catheter was easily withdrawn from the superior pulmonary vein Therefore we cannot fully exclude the possibility that mural thrombus elsewhere in the atrium was also a potential source of cerebral embolization However no detectable embolization occurred after removal of the catheter

Left atrial catheter retention with subsequent systemic embolization is a potential complication of this form of postoperative hemodynamic management In fact many now favor the preoperative placement of Swan Ganz pulmonary artery lines for the indirect measurement of left heart filling pressure

We would recommend that if a left atrial catheter is used an echocardiogram be performed preoperatively and in the early postoperative period In this way the baseline appearance of the left atrium and the echo characteristics of the intra atrial catheter can be established We have been unable to determine the position of these faintly radiopaque catheters on chest x rays done in the postoperative period and do not recommend reliance on chest roentgenography in these cases

If an attempt to remove a left atrial catheter is unsuccessful an echo study should be repeated to inspect the left atrium for signs of retention of the line From our experience these catheters are remarkably echo dense in spite of their narrow diameters Demonstration of this foreign body within the left atrium would justify and indeed make mandatory repeat thoracotomy for removal of the catheter

Although M Mode echocardiography easily demonstrates the presence and location of intracardiac catheters it is anticipated that two dimensional sector scanning will be used to provide even more detailed pictures of these foreign bodies in the future

Summary

An 18 year old woman underwent the repair of traumatic lacerations of the mitral valve tricuspid valve and interventricular septum At the time of surgery an indwelling left atrial catheter was placed for postoperative hemodynamic management An attempt to remove the catheter completely several days following surgery was unsuccessful but it was initially assumed by the surgeon that the tip of the catheter had been withdrawn from the left atrium When the patient developed neurologic signs suggesting a cerebral embolism an echocardiogram was performed Echo demonstration of the catheter in the left atrium led to repeat thoracotomy for removal of the retained line

Baseline echocardiograms are indicated in cardiac surgical patients with indwelling left atrial catheters and echo study can be diagnostic if catheter retention occurs

REFERENCES

1 Righetti A Crawford M H O Rourke R A Daily P O and Ross J Echocardiographic and roentgenographic determination of left ventricular size after coronary arterial bypass graft surgery Chest 72 455 1977
2 Fernando H A Friedman H S Lajam F, and Sakurai H Late cardiac tamponade following open heart surgery Detection by echocardiography Ann Thorac Surg 24 174 1977
3 Kisslo J Wofson S Ross A Pasternak, R Hammond G and Cohen L S Ultrasonic assessment of left ventricular function following aortocoronary saphenous vein bypass grafting Circulation 47 and 48(Suppl III) 156 1973
4 Righetti, A Crawford M H O Rourke R A Schelbert H Daily P O, and Ross J Interventricular septal motion and left ventricular function after coronary bypass surgery Evaluation with echocardiography and radionuclide angiography Am J Cardiol, 39 372 1977
5 Brodie B R Grossman W McLaurin L Starek P and Craige E Diagnosis of prosthetic mitral valve malfunction with combined echo-phonocardiography Circulation 53 93 1976
6 Levisman J J Echoes from Swan Ganz catheter Chest 70 1 1976
7 Charuzi Y Kraus R and Swan H J C Echocardiographic interpretation in the presence of Swan Ganz intracardiac catheters Am J Cardiol 40 989 1977

Morbidity associated with anomalous origin of the right coronary artery from the left sinus of Valsalva

William Benge M D
James B Martins M D
David C Funk M D
Iowa City Iowa

Anomalous origin of the right coronary artery from the left sinus of Valsalva is considered benign clinical sequelae have generally been related only to the coexistence of atherosclerosis [3] Selective catheterization of the anomalous artery has been reported in two patients with angina like chest pain but no abnormalities other than the anomalous origin were noted [4] A recent review of coronary anomalies notes that the "hemodynamic significance has not yet been firmly established in right coronary origin from the left sinus of Valsalva The case that follows suggests that this anomaly even without atherosclerosis may be associated with significant cardiovascular morbidity and that compression of the early portion of the artery may be responsi

Case report

J A C a [illegible]-year-old man had a five minute episode of anterior chest pain followed two days later by several syncopal episodes On admission to another hospital he was noted to have second-degree A V block which progressed to third degree A V block requiring a permanent pacemaker The ECG showed marked T wave inversion in inferior and lateral precordial leads (Fig 1) Serum levels of cardiac enzymes were normal.

He was referred to the Veterans Administration Hospital in Iowa City Iowa, for evaluation of the heart block He had felt well except for an occasional chest pain of short duration at rest On physical examination BP was 110/70 mm Hg pulse

From the Cardiovascular Division Department of Internal Medicine University of Iowa Hospitals and Clinics, and the Veterans Administration Hospital, Iowa City

Received for publication Oct 10 1978

Accepted for publication Feb 1979

Reprint requests James B Martins M D Cardiovascular Division University of Iowa Iowa City Iowa [illegible]

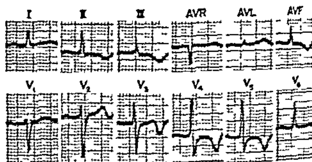


Fig 1 Electrocardiogram at initial hospitalization.

at rest was 72 beats per minute and regular With walking the pulse increased to 84 beats per minute There was a pulse generator in the right infraclavicular region Cardiac examination revealed a normal S normal S and an S_3 gallop Remainder of the examination was unremarkable The ECG showed a ventricular pacemaker firing at 72 beats per minute with 100% capture A chest x ray showed the permanent transvenous pacemaker in the right ventricular apex. A thallium scan with exercise revealed hypoperfusion of apical and posterior septal regions Delayed views were not obtained.

Cardiac catheterization was performed to determine the etiology and location of the conduction system disease Electrophysiologic studies revealed sinus rhythm at a rate of 7[illegible] beats per minute Second-degree A V block with Wenckebach phenomenon occurred with an atrial pacing rate of 81 beats per minute Following 1 mg of intravenous atropine sulfate second-degree A V block with the Wenckebach phenomenon occurred at an atrial pacing rate of 155 beats per minute H V intervals at all levels of atrial pacing before and after atropine were normal. The left ventriculogram showed an ejection fraction of 38% with apical hypokinesis and posterior wall dyskinesis Retrograde femoral coronary arteriograms revealed a normal, nondominant left coronary artery The right coronary artery could not be selectively catheterized in spite of multiple attempts with a variety of catheters. On aortic root injection the right coronary artery was seen to originate from the left sinus of Valsalva and crossed the aortic root

0002-8703 80/010096 + 0[illegible]00/0

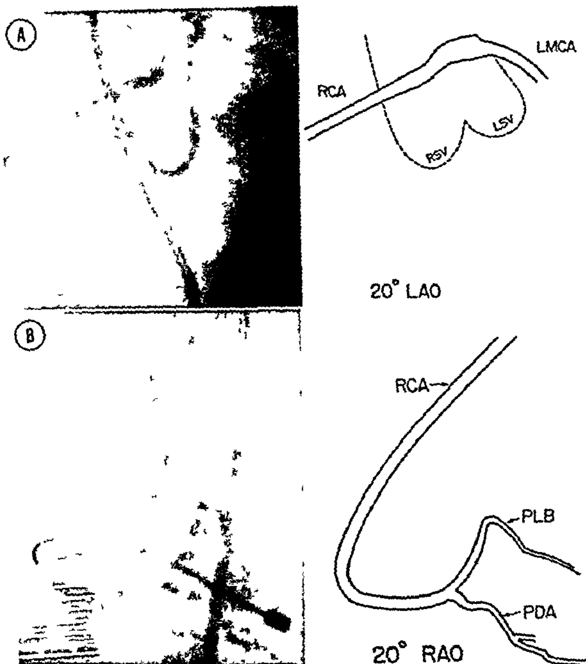


Fig 2 Coronary arteriograms and corresponding drawings of the anomalous right coronary artery in the patient discussed *A* 20 degree LAO projection *B* 20 degree RAO projection Note the proximity of the right and left coronary artery ostia (A permanent pacemaker catheter is present) *LMCA* = left main coronary artery *PDA* = posterior descending artery *PLB* = posterolateral branch of the right coronary artery

anteriorly but was not outlined sufficiently for detailed analysis

On the patient s return to the catheterization laboratory selective catheterization of the anomalous right coronary artery was obtained using a No 1 left Amplatz coronary catheter with a Seldinger femoral artery approach A dominant nondiseased right coronary artery arising from the left sinus of Valsalva was demonstrated (Fig 2) The A V nodal artery arose from the anomalous right coronary artery The first portion of the anomalous artery could be seen to be transiently narrowed by 20% during systole (Fig 3)

Discussion

The patient described here had significant morbidity associated with anomalous origin of the right coronary artery from the left sinus of Valsalva Dyskinesis of the left ventricular wall in

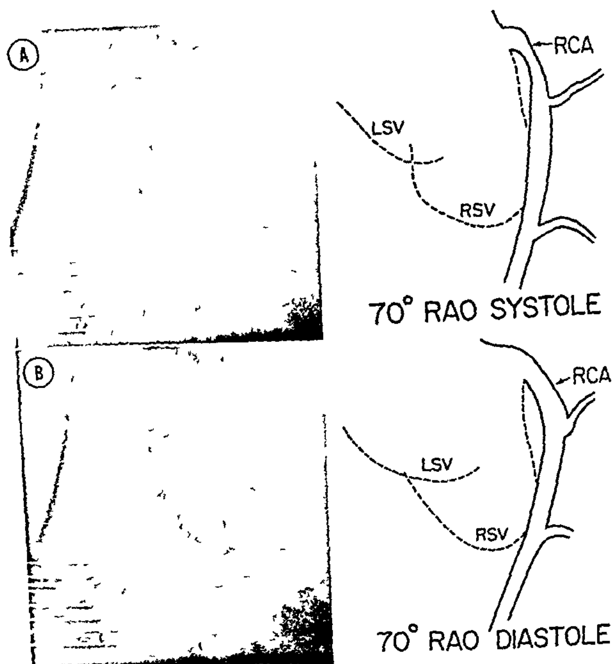


Fig 3 Forty five degree RAO coronary arteriograms with corresponding drawings of the anomalous right coronary artery in the patient during *A* systole and *B* diastole Note the narrowing during systole Simultareous electrocardiogram is in the left lower corner of each frame

the distribution of a nondiseased anomalous right coronary artery occurred in a 25 year old man Selective angiographic demonstration of the anomalous artery was essential to determine the presence or absence of luminal narrowing in the anomalous artery

Anomalous origin of the coronary arteries has been reviewed by many authors The incidence of all coronary anomalies ranges from 0 3% to 1 2%[1-3] and anomalous origin of the right coronary artery from the left sinus of Valsalva is reported to constitute from 6% to 27% of all coronary anomalies[9,10]

There is apparently no relationship between the type of anomaly and the presence or degree of coronary sclerosis Moreover there is no predilection for atherosclerosis in anomalous coronary arteries[1-3] Liberthson and associates[2] reported four patients with coronary atherosclerosis and anomalous origin of the right coronary artery from the left sinus of Valsalva None had atherosclerosis in the anomalous artery[2]

The consensus has been that anomalous origin of the right coronary artery in the absence of arteriosclerotic lesions is benign[1,3 ... 10,1] Thompson and colleagues reported two cases with probable angina and Cheitlin and co workers[6] briefly mention a 30 year old man with a nondiseased anomalous right coronary artery who had evidence of an inferior myocardial infarction by ECG and enzymes The case presented here is the first detailed report in which anomalous origin of the right coronary artery from the left sinus of Valsalva was associated with significant morbidity in the absence of an associated atherosclerotic lesion

How could morbidity occur with this anomaly in the absence of atherosclerosis? In patients where an anomalous main left coronary artery originates from the right sinus of Valsalva and courses between the aorta and pulmonary artery significant morbidity and mortality occur[1,1,1] Atherosclerosis is not found in most patients who die from this anomaly The etiology of this phenomenon is not known but two major explanations have been proposed First the aorta and pulmonary artery might expand sufficiently with exercise to compress the coronary vessel passing between them Patients have been described in whom myocardial infarction has occurred when a nonatherosclerotic left coronary artery with anomalous origin follows a course anterior to the pulmonary artery or posterior to the aortic root and therefore could not be compressed between the great vessels This fact suggests that other mechanisms may also be responsible for morbidity in patients with anomalous aortic origin of the coronary arteries

Closure of the anomalous ostium within the aortic wall may be a more tenable mechanism for infarction and sudden death[6] With expansion of the aorta during the systolic pressure rise with exercise or hypertension a slit like arterial segment coursing tangentially through the aortic wall could easily be narrowed or occluded Systolic compression of the anomalous artery appeared to occur in our patient with a nondiseased anomalous right coronary artery but was not severe at rest as judged by the extent of narrowing seen (Fig 3) Either or both of these mechanisms might have been responsible for the morbidity reported herein

While sudden death has not been reported with anomalous right coronary artery from the left sinus of Valsalva this anomaly does appear to produce morbidity independent of atherosclerotic sequelae and may not be a totally benign lesion Selective demonstration of the anomalous right coronary artery is necessary to diagnose correctly and treat patients with chest pain and this anomaly In the absence of atherosclerosis surgical revision of an anomalous aortic origin of a coronary artery has been performed in one patient with anomalous left main coronary artery from the right sinus of Valsalva which had been associated with syncope and cardiac arrest Whether surgical revision might be beneficial in a patient with anomalous right coronary origin from the left sinus of Valsalva remains to be demonstrated

Summary

Anomalies of the coronary arteries occur infrequently but can have major clinical consequences Many reports have described an association between sudden death and origin of the left coronary artery from the right sinus of Valsalva but origin of the right coronary artery from the left sinus of Valsalva is thought to be benign Herein we describe a patient in whom anomalous origin of the right coronary artery from the left sinus of Valsalva was associated with significant cardiovascular morbidity A 25 year old man developed complete heart block and myocardial infarction in the distribution of a dominant anomalous right coronary artery free of atherosclerotic lesions Systolic compression at the origin of the anomalous artery was demonstrated The left coronary artery was normal We conclude that anomalous origin of the right coronary artery from the left sinus of Valsalva may be associated with significant cardiovascular morbidity in the absence of atherosclerosis

We gratefully acknowledge the secretarial assistance of Ms Debbie Mansure and the expert preparation of illustrations by Mr Louis Facto

REFERENCES

1 Chaitman, B R Lesperance J Saltiel J and Bourassa M G Clinical angiographic and hemodynamic findings in patients with anomalous origin of the coronary arteries Circulation 53 122 1976

2 Liberthson R R Dinsmore R E., Block, P C Pohost G M and Strauss H W Myocardial compromise and sudden death in aberrant coronary origin from the aorta (Abstract) Am J Cardiol 41 358 1978

3 Liberthson R R Dinsmore R E. Bharati, S Rubenstein J J Caulfield J Wheeler E O., Hawthorne J

W., and Lev M Aberrant coronary artery origin from the aorta Circulation 50 774 1974
4 Thompson S I Vieweg W V R Alpert J S and Hagin A D Anamolous origin of the right coronary artery from the left sinus of Valsalva with associated chest pain report of two cases Cathet Cardiovasc Diagn 2 397 1976
5 Levin D C Fellows K E and Abrams H L Hemodynamically significant primary anomalies of the coronary arteries Circulation 58 25 1978
6 Cheitlin M D DeCastro C M and McAllister H A Sudden death as a complication *of anomalous left coro*nary origin from the anterior sinus of Valsalva Circulation 50 780 1974
7 Alexander R W and Griffith G C Anomalies of the coronary arteries and their clinical significance Circulation 14 800 1956
8 Ogden J A Congenital anomalies of the coronary arteries Am J Cardiol. 25 474 1970
9 Kimbiris D I bandrian A S Bemis C E and Segal B S Anomalous aortic origin of coronary arteries (Abstract) Clin Res 243A April 1978
10 Engel H J Torres C and Page H L Jr Major variations in anatomical origin of the coronary arteries Angiographic observations in 4 250 patients without associated congenital heart disease Cathet Cardiovasc Diagn 1 157 1975
11 Zumbo O Fani K Jarmolych J and Daoud A S Coronary atherosclerosis and myocardial infarction in hearts with anomalous coronary arteries (Abstract) Lab Invest 14 571 1965
12 Rhatigan R M and de la Torae A Anomalous origin of the right coronary artery Vasc Surg 5 196 1971
13 *Cohen L. S and Shaw L. D Fatal myocardial infar*tion in an 11 year old boy associated with a unique coronary artery anomaly Am J Cardiol 19 420 1967
14 Benson P A Anomalous aortic origin of coronary artery with sudden death Case report and review Am HEART J 79 254 1970
15 Pachinger O M VandenHoven P and Judkins, M P Single coronary artery—a cause of angina pectoris, *Europ J Cardiol 2/2 161 1974*

Current concepts of left ventricular relaxation and compliance

Basil S Lewis M D M R C P F C P (SA)
Mervyn S Gotsman M D F R C P F A C C
Jerusalem Israel

Cardiac relaxation is impaired in many cardiac disorders and is the subject of extensive investigation As ventricular relaxation proceeds during diastole the heart fills with a given stroke volume and it is this volume which is ejected during the succeeding systole Abnormal ventricular relaxation is thus necessarily accompanied by alteration in systolic cardiac performance while the consequences proximal to the abnormal cardiac chamber include elevated venous pressures venous distension and the clinical signs and symptoms of congestive heart failure

Relaxation is an active process At a biochemical level important events occur and there are energy dependent intracellular shifts of Ca ions At a mechanical level obstruction to left ventricular inflow produces in the experimental animal a negative ventricular pressure with respect to the atmosphere and the pressure–volume (P–V) curve falls to below the zero pressure line at small ventricular volumes in keeping with the old suction theory of ventricular filling

This review will consider current concepts of cardiac relaxation biochemical aspects aspects of muscle mechanics and problems in the intact heart It will include a review of methods and techniques for the assessment of left ventricular (LV) relaxation and compliance abnormalities of relaxation in different cardiac diseases and the significance of abnormalities of compliance in the clinical situation

From the Cardiology Department Hadassah Hospital, and the Hebrew University Jerusalem Israel

Supported by a grant from the United States Public Health Service under National Library of Medicine P L 480 Agreement 06-501 1 with the Israel Journal of Medical Sciences

Received for publication Oct 10 19 8

Reprint requests Dr B S Lewis Cardiology Department Hadassah Hospital P O Box 499 Jerusalem Israel

Biochemical aspects

The biochemical mechanism of muscle contraction at sarcomere level is shown diagramatically in Fig 1 Electrochemical activation of the cell is followed by transfer of Ca ions into the cell across the cellular membrane from the extracellular space and from the lateral sacs of the sarcoplasmic reticulum (SR) This Ca flux marks the onset of the *contraction process* The Ca binds to the intracellular proteins troponin tropomyosin the contractile proteins actin and myosin interact and the myofilaments slide on each other to produce sarcomere shortening and generation of tension The process of shortening is physically the result of cross bridge formation or of electrostatic forces which are generated within the sarcomere The intracellular Ca rise precedes the build up of tension* and declines long before contractile tension declines it is not certain what sustains the force of contraction thereafter—quick release shortening experiments in the barnacle fiber show that sudden muscle shortening produces a small elevation in the declining Ca transient but muscle shortening also causes a decrease in the muscle s ability to generate force (deactivation theory) There is clearly a relation between mechanical and biochemical elements and mechanical shortening may be a factor in the initiation of relaxation

The precise mechanisms involved in *relaxation of cardiac muscle* are not certain—relaxation seems to be governed by the interaction of an activation controlled and a load controlled decay mechanism the relative contributions of which differ among different animal species

The transition from the active to the resting state requires a reduction in cytosolic ionised Ca concentration and this is achieved by (1) a rapid sequestration of Ca into the SR (2) the

DEPOLARIZATION
Ca
SL
Na⁺K⁺–ATPase
Ca Ca Ca Ca
Ca
Ca
Ca
TROPO
CONTRACTION (ACTIN + MYOSIN)
Ca
SR
Ca
RELAXATION
?
MT
TROPO troponin tropomyosin system
SR sarcoplasmic reticulum
SL sarcolemma
MT mitochondrion

Fig 1 Schematic diagram to show movement of Ca ions in the cell during contraction and relaxation Depolarization of the cell is followed by movement of Ca into the cell release of Ca from storage sites and binding of Ca to troponin leading to contraction During relaxation Ca reuptake by the sarcoplasmic reticulum (SR) and possibly by the mitochondria (MT) removes most of the free Ca from the cell (Reproduced from Schwartz A by permission of The Williams & Wilkins Company)

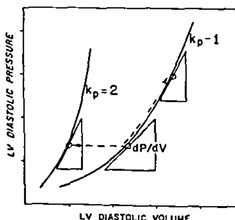


Fig 2 Diastolic left ventricular pressure-volume (P–V) curves Chamber stiffness of the ventricle is the change in pressure for a change in volume and measured as a tangent to the P-V curve is given by dP/dV Volume loading of the LV shifts the patient to a steeper part of the P-V curve and dP/dV (chamber stiffness) increases The chamber stiffness modulus (slope of the curve) remains k 1 Chamber stiffness (dP/dV) also increases if the modulus of chamber stiffness increases and the curve becomes more steep (k 2) (Reproduced from Gaasch and colleagues by permission of the *American Journal of Cardiology*)

return of some Ca to the extracellular space and (3) Ca buffering mechanisms

1 Accumulation of Ca by the SR is a rapid energy dependent process energy being derived from the hydrolysis of ATP via a Ca activated ATP ase in the limiting membranes of the SR' Nayler and Williams[4] have suggested that impaired relaxation in heart muscle may theoretically result from an inadequate supply of ATP Ca overload failure of the Ca activated ATP ase enzyme leakage of Ca from the SR or from failure of the cell to return Ca back into the extracellular phase There is reversible failure of relaxation (with a resulting rise in resting cardiac tension) in the presence of *hypoxia* where there is deficient mitochondrial function and inadequate ATP substrate to drive the ATP ase enzyme of the SR Ca reuptake system Resting muscle tension also increases in *ouabain* contractures due to diminished tissue stores of ATP and a later rise in tissue Ca Some *toxins* causing cardiac arrest in systole make the SR leaky to Ca

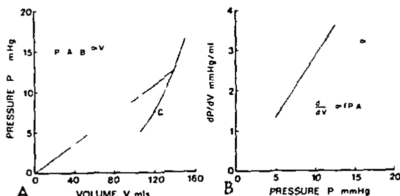


Fig 3 Pressure–volume relations. *A* The P–V relationship at end-diastole (ed) is exponential (slope α) *B* Relationship between pressure P and dP/dV (chamber stiffness) The curve is linear with slope α (modulus of chamber stiffness) (Reproduced from Mirsky I by permission of *Progress in Cardiovascular Diseases*)

The system is also pH dependent Moreover there is evidence that a primary inotropic effect of adrenaline apart from its effects on membrane conductance (where it increases conductance during the plateau phase to elevate the plateau potential and increase action potential duration effects which increase tension in frog ventricle) may be to stimulate sequestration of Ca in the cell via a cyclic amp mechanism—i e to increase relaxation of tension to facilitate recirculation of the Ca pool The effect is mediated by beta adrenergic receptors and can be blocked by substances which block the beta receptors

2 Extracellular extrusion of Ca is related to the sarcolemmal Na /Ca exchange mechanism In frog heart experiments the rate of relaxation decreases with an increase in intracellular Na and a fall in the Na gradient [1]

3 In addition to the rapid mechanisms permitting relaxation after each contraction there are cellular Ca buffers located in the mitochondria the SR and possibly in the troponin and other regulatory or contractile proteins as well as in glycoproteins and glycolipids of the basement membrane

Mechanical factors which may be important in relaxation are the decreased force generated by the same calcium at shorter muscle lengths (deactivation) and the relations between peak tension and the rate of relaxation If sarcomere length is held constant during early relaxation developed tension falls more rapidly than when over all muscle length is kept constant Moreover there is non uniformity in sarcomere length and sarcomere length dispersion increases in the interval between contractions without a change in resting tension [1]

Aspects of relaxation and compliance in the intact heart

The problem of cardiac relaxation in the intact heart revolves essentially around the diastolic stiffness properties of the left ventricle (LV) The stiffness or compliance of the LV may be considered at two levels (1) at the level of the intact pumping chamber—the situation in the intact animal and in the intact patient (LV chamber stiffness or compliance) and (2) at the level of a unit of myocardium (muscle stiffness and muscle compliance)

Chamber compliance of the left ventricle Left ventricular filling takes place in diastole and as the LV fills its pressure rises Studies of ventricular compliance were originally based on measurements of LV end diastolic pressure (LVEDP)[1] and later on the relationship of the LVEDP to end diastolic volume (V) on the total pressure change during diastole (ΔP) or on change in pressure (ΔP) for given change in ventricular volume (ΔV) *LV stiffness* is given by the change in pressure for a given change in volume ($\Delta P/\Delta V$) and *LV compliance* or *distensibility* by its reciprocal $\Delta V/\Delta P$ while specific compliance is calculated by correcting for LV cavity size ($\Delta V/V\Delta P$) These measurements can be made as the *mean* change over the whole of diastole (i e as a *chord* to the diastolic P–V curve) or by considering limiting boundaries ($\Delta V \rightarrow 0$) and by measuring the slope as a *tangent* to the curve at any point during diastole dP/dV therefore gives instantaneous operative volume stiffness and dV/dP gives instantaneous chamber distensibility or chamber compliance Since the LV pressure–volume curve is in general terms exponential (Fig 2) dV/dP decreases as ventricular volume increases

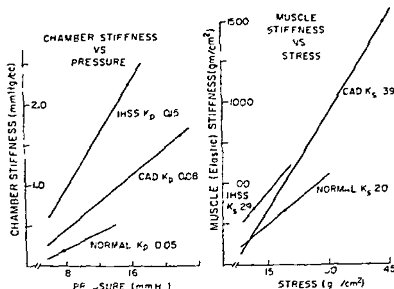


Fig 4 Relations between "chamber stiffness" and pressure (*left hand panel*) and "muscle stiffness" and stress (*right hand panel*) in a normal subject patient with coronary artery disease (*CAD*) and hypertrophic cardiomyopathy (*IHSS*) The modulus of chamber stiffness k is increased in CAD and increased further in IHSS When muscle stiffness is considered however the modulus k is highest in CAD and only mildly increased in IHSS Operative muscle stiffness is normal in IHSS since actual stress is low Both operative stress and muscle stiffness are very high in CAD (Reproduced from Gaasch and colleagues by permission of the *American Journal of Cardiology*)

so that simple volume loading of an otherwise normal ventricle causes a decrease in LV compliance (or increase in stiffness) and an increased end-diastolic pressure [1] The rate of change of chamber stiffness with increasing P (*the modulus of chamber stiffness*) is given by k_p or α (Figs 2 and 3) Algebraically this may be written

$$P = be^{kV}$$
$$\ln P = kV + \ln b$$
$$k = (\ln P - \ln b)/V$$

An increase in k_p occurs in cardiac disease associated with LV hypertrophy and/or fibrosis An increase in k_p means that the ventricle is more stiff at any given ventricular volume and the diastolic ventricular pressures increase A decrease in LV compliance (increase in stiffness) may be the consequence then of (1) an increase in ventricular volume or (2) of a change in the modulus of chamber stiffness (k_p) or (3) a combination of the two mechanisms (Fig 2) (Table I) On the other hand a decrease in the modulus of chamber stiffness occurs in chronic LV volume overload—e g., chronic aortic incompetence mitral incompetence congenital VSD k_p decreases and large volume loads are handled at a relatively low end-diastolic pressure The mechanism of the change is not clear it may be related to myocardial fiber slippage reduplication of sarcomeres (in series and in parallel) or to pericardial changes [2]

Muscle stiffness and muscle compliance The stiffness properties of the myocardium are described by the stress–strain relations of a unit of myocardium [1,4] The mathematics and calculation of muscle stiffness are analogous to that of chamber (volume) stiffness but stress is used instead of pressure and strain for volume The instantaneous *stiffness* of a unit of myocardium is given by the tangent to the stress–strain curve (E or tangent modulus) The *modulus of muscle stiffness* (k) is the rate of change of E for an increase in stress (Fig 4)

The distinction between LV chamber stiffness and muscle stiffness is important since operative chamber stiffness depends not only on the stiffness of the muscle but also on ventricular loading conditions and ventricular muscle mass. An increase in muscle mass increases operative chamber stiffness filling is impaired in the hypertrophied ventricle and diastolic pressures may be high despite normal or relatively normal stiffness properties of each unit of myocardium The difference between chamber and muscle stiffness is shown in Fig 4 for patients with hypertrophic cardiomyopathy (HOCM) coronary artery disease (CAD) and in a normal subject [2] In HOCM chamber stiffness is high and the curve is very

steep (k_p very high) while in CAD chamber stiffness and its modulus k_p are increased less When *muscle* stiffness E and its modulus k are considered however it is clear that in HOCM k_s is only slightly increased while in CAD k is twice normal and muscle stiffness is very high It follows then that in HOCM k_p is high and the diastolic P-V curve is steep because of ventricular hypertrophy and a change in cavity geometry in CAD the steep P-V curve is the consequence of an increase in intrinsic muscle stiffness the result of ventricular fibrosis

The LV volume-mass ratio

The normal LV volume/mass ratio (V/M ratio) is just less than 1 0 (LVEDV 70 ml /M LV wall mass 90 g /M²) It has been shown that myocardial stiffness and its modulus k may be estimated from the product of k_p and the V/M ratio In HOCM k_p is high there is great muscle hypertrophy with a low V/M ratio and muscle stiffness (k) may be normal In contrast in patients with coronary artery disease k_p is again high but the normal or near normal V/M ratio suggests that muscle stiffness and k are high because of ventricular fibrosis in the region of myocardial damage

Chronic volume loading is associated with a normal V/M ratio k_p is reduced presumably the result of a decreased k Acute volume loading is *accompanied by a high LVEDP little change in* k_p an increase in V/M and a high k These data have been well summarized by Gaasch and colleagues

LV compliance throughout diastole

Until recently most studies described LV pressure-volume and stress-strain relations at selected points at end diastole at early and end diastole or at different points during diastole It had been assumed that the LV diastolic P-V relationship was exponential but while data taken from a single point at end diastole may produce exponential curves in animal studies and in inter or intra patient studies these data apply to end diastole only It is not necessarily true that the LV P-V curve is exponential throughout diastole On the contrary the tangent modulus E changes markedly during the different phases of diastole with an extremely low value when calculated in mid diastole during the slow filling phase [1] Present studies are directed at characterizing the stiffness properties of the myocardium during the different phases of ventricular diastole

Table 1 Some diseases associated with decreased LV compliance

1 *Increased LV volume (k unchanged)*
  - a Fluid overload due to anaemia renal failure over transfusion
  - b Valvular incompetence (mitral and especially aortic)
  - c Left to-right shunts or arteriovenous fistulas

2 *Increased modulus of chamber stiffness (k_p)*
  - a Increased stiffness of the LV chamber due to geometrical changes of ventricular hypertrophy (AS HOCM hypertension)
  - b Abnormal intrinsic muscle stiffness (k_s)
    - –damaged LV muscle with scar tissue (coronary artery disease LV fibrosis)
    - –cardiac infiltrative disorders (amyloidosis)
    - –*pericardial changes (constrictive pericarditis)*

In chronic volume overload changes in the modulus of chamber stiffness k_s may offset the expected increase in LV stiffness due to th increase in ventricular volumes.

Other measurements of ventricular relaxation

1 Negative LV dp/dt The peak rate of fall of LV pressure (peak neg dp/dt) usually occurs during the isovolumic relaxation period and has been used as a measurement of early diastolic relaxation but depends on end systolic volume and pressure [1] The time course of relaxation (T) derived from the rate constant of the exponential pressure decline during isovolumic diastole subsequent to the occurrence of peak neg dp/dt may be a better index of early diastolic relaxation It seems to be independent of peak systolic pressure end systolic volume and fiber length [31] Both peak neg dp/dt and T are abnormal in patients with coronary artery disease during pacing induced angina [3] [4] and suggest that impaired early ventricular relaxation may be responsible for the rise in end diastolic pressure which occurs later in diastole Peak neg dp/dt is related to peak pos dp/dt and is also abnormal in congestive cardiomyopathy where it has been suggested that both impaired ventricular contraction and relaxation are important in the pathogenesis of the disease [37]

2 Rate and pattern of LV filling and the isovolumic relaxation period The normal LV relaxes rapidly in early diastole so that a large volume of blood enters immediately after mitral valve opening By the time the 0 point is reached up to 50 per cent of ventricular filling may have

occurred another 30 to 40 per cent occurs by the end of the rapid filling phase, there is little change during slow filling and atrial systole delivers the last 5 to 10 per cent of the volume filling the LV[3] The instantaneous LV filling rate can be measured from digitization of the angiocardiogram or echocardiogram to show abnormalities both in the timing and rate of ventricular filling The subject has been studied by Gibson and colleagues who have shown abnormal LV filling rates and times and abnormal wall thinning in patients with abnormal LV chamber compliance (hypertrophic cardiomyopathy) These authors have also drawn attention to the presence of abnormal ventricular wall movement during the isovolumic relaxation period in patients with coronary artery disease pa tients with CAD and regional asynergy have important changes in LV diameter with abnormal inward or outward movement of the ventricular wall during the isovolumic relaxation period depending on whether the abnormal or normal segment is studied Displacement-diameter loops are constructed from the echo and apexcardiogram by digitizing the tracings and computer processing

Effect of the pericardium and right ventricle

Studies of the diastolic properties of the LV in the intact heart must take into account the effect of changes in right heart function and the pericardium Right ventricular abnormalities and right ventricular hypertrophy are accompanied by changes in septal and free LV wall thickness and by abnormal left ventricular pressure-volume relations Similarly, pericardial disease (effusion or constriction) causes abnormal function of the LV in diastole The importance of the pericardium and the right ventricle is not certain in primary diseases of the left ventricle but may be greater than thought previously Indeed in patients with left ventricular volume overload the difference between the steep pressure-volume curve and very high LV end diastolic pressure of the acute situation (e g acute AI) and the flatter P-V curve of chronic disease may be that of pericardial adaptation to the increased volume over a period of time Similarly a large pericardial effusion (1 000 to 2 000 ml) may be tolerated reasonably well if it accumulates over a period of weeks to months but acute cardiac tamponade occurs if a smaller volume of fluid accumulates rapidly In patients with congestive cardiomyopathy, some improvement in the clinical state has been reported after pericardiectomy

Clinical methods in studies of ventricular compliance

Calculation of the indices of chamber and muscle stiffness requires simultaneous measurement of ventricular geometry (cavity size shape and wall thickness) and intraventricular pressure This means that at present an invasive procedure is required *Intracardiac pressure* should be measured using a catheter tip micromanometer The frequency response of a good fluid filled catheter manometer system may be flat to 15 to 20 Hz but LV pressure falls rapidly in early diastole to 2 to 5 mm Hg at the 0 point Any error due to overshoot or resonance is important and significant at this level of pressure Measurements of end diastolic pressure are more accurate but we believe that all modern detailed studies of diastole should be made with the greatest possible accuracy using an intracardiac micromanometer

Accurate measurement of LV geometry and LV volume change is also difficult *Angiocardiography* provides details of LV cavity shape and size Measurements of free wall thickness can be obtained Both uniplane and biplane methods have been used but it must be remembered that studies based on single plane angiography are less accurate especially at beginning diastole and in patients with coronary artery disease and regional ventricular asynergy Moreover angiography opacifies the LV for only 5 to 10 beats and respiratory maneuvers during filming and the rapid injection of contrast medium may alter ventricular dynamics The procedure cannot be repeated more than once or twice *Echocardiography* on the other hand provides accurate measurement of ventricular cavity dimensions and wall thickness (including both septum and posterior free wall) does not upset the patient's hemodynamic state and can be repeated at will The M mode echo however, provides limited views of the left ventricle and does not provide data relating to over all cavity shape information which is necessary for the calculation of wall stress Cross sectional echocardiography may be useful in studies of LV pressure-volume and stress-strain relations but the quality of the image must be adequate to identify accurately

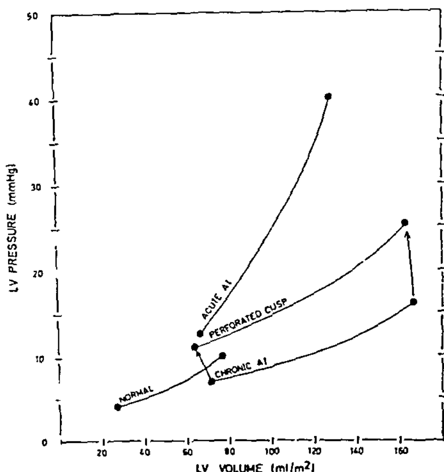


Fig 5 Diastolic pressure–volume curves of the left ventricle (LV) in aortic incompetence (AI) plotted as a chord from the 0 point to LV end-diastolic pressure In acute AI the patient is shifted up a normal P-V curve and end-diastolic pressure and dP/dV are very high In chronic AI the modulus of chamber stiffness has decreased the curve is less steep and a large volume load is handled at a relatively low end diastolic pressure and dP/dV (Reproduced from Lewis B S and associates with permission of *Israel Journal of Medical Sciences*)

and specifically both endo and epicardium

Lastly the importance of recording ventricular pressure and volume simultaneously should be noted Earlier studies which relate end systolic volume to the 0 point in the LV pressure pulse tracing underestimate LV volume at this time since appreciable left ventricular filling occurs immediately after mitral valve opening

Abnormal geometry

Calculation of wall stress requires detailed information relating to LV cavity geometry The left ventricle has been likened to an ellipsoid and several formulas have been derived for wall stress most authors using a thick walled model in which shear stresses and bending moments are neglected It seems preferable to base a model on large deformation theory The use of simpler formulas using spherical geometry may provide similar results in any event the shape of the ventricle changes during systole and diastole and especially so in patients with cardiac dilatation or regional ventricular dysfunction Moreover fiber orientation is extremely variable at different sites in the ventricular wall and there is at present no way to take this into account in the intact patient the distribution of muscle fiber stress from epicardium to endocardium is not necessarily linear and predictable Computer analysis has greatly facilitated studies of these problems in analyses of ventricular diastole The computer has been invaluable in modelling in making calculations from digitized data and in the development of mathematical models using finite element theory which may be useful in a more detailed analysis of regional muscle function[10 s 55]

Left ventricular compliance in clinical cardiac disease

Left ventricular volume overload

1 Acute volume overload Chamber compliance is greatly decreased as the ventricle unprepared for the sudden large volume load is shifted upwards along its pressure-volume curve (Fig 5) In acute aortic incompetence the end diastolic pressure increases markedly to 50 to 60 mm Hg[54] and the patient develops severe left heart failure with pulmonary edema In acute mitral incompetence there is again a significant decrease in LV compliance as ventricular volume increases the end diastolic pressure is usually lower than in acute aortic incompetence since systolic ventricular emptying is facilitated in acute mitral incompetence by the sudden decrease in ventricular afterload There is less information regarding *muscle stiffness* in acute aortic or mitral incompetence The cavity dilates the wall is thin and muscle fiber stress is high The tangent modulus E is high since operative stress is increased The volume-mass ratio increases k is probably normal

2 Chronic volume overload In chronic rheumatic mitral and aortic incompetence the ventricle adapts with a decrease in the modulus of chamber stiffness (k_p) so that large volumes are handled at relatively low end diastolic pressures[55] (Fig 5) chronic aortic or mitral incompetence may be well tolerated clinically for many years e precise mechanism for the change in chamber ffness is uncertain it may be due to changes in e myocardial fiber arrangement or to pericar ıal adaptation It has been suggested that *muscle stiffness* should increase with ventricular fibrosis and hypertrophy

Left ventricular pressure load and ventricular hypertrophy Studies have been made in aortic stenosis and in hypertrophic cardiomyopathy (HOCM IHSS) LV hypertrophy is accompanied by an important increase in the modulus of LV *chamber stiffness* (k_p) The slope of the P-V curve is steep and operative end diastolic pressure and compliance are high

Measurements of *muscle stiffness* provide interesting results While some patients with aortic stenosis have an important increase in muscle stiffness k is only moderately abnormal in other patients despite a large increase in LV chamber stiffness ' ^ This may be predicted from the decrease in the LV volume/mass ratio which occurs in aortic stenosis and in HOCM Operati e stress may be low in patients with HOCM The distinction between measurements of chamber compliance and muscle compliance is therefore crucial in modern studies of ventricular relaxation and diastole (Fig 4)

Coronary artery disease Ventricular damage is segmental in CAD measured changes in over all chamber stiffness are the result in changes in *muscle stiffness* in the abnormal ischemic zone(s) in the boundary layer and in the remaining healthy myocardium Myocardial ischemia interferes with myocardial relaxation muscle stiffness and its modulus k increase and total ventricular *chamber compliance* falls There may be a shift to a steeper P-V curve (increased k_p) ' or the whole LV P-V curve moves upwards ' resulting in a high end diastolic pressure In pacing induced angina there is a fall in neg dp/dt " ' –ie an abnormality of early diastolic relaxation–and this contributes to the higher diastolic pressures later in diastole Similar events occur after myocardial infarction but in angina pectoris the changes are reversible In myocardial infarction an early *increase* in compliance has been observed in some experimental animal studies using sudden coronary occlusion This may be due to stress relaxation[57] or simply to the abrupt cut off of coronary blood flow with a fall in myocardial turgidity[58 5] In the days following myocardial infarction there is stiffening of the infarcted area to improve the mechanical disadvantage of the dyskinetic area during systole stiffness is high 5 to 6 days after the infarct and the high muscle stiffness is maintained as permanent fibrosis of the infarcted area occurs LV chamber stiffness and LV P-V relations usually remain abnormal after myocardial infarction if the infarcted area is sufficiently large [6] Fibrous aneurysms resected from human left ventricle have higher stiffness values than do muscular aneurysms

Myocardial disease In *primary myocardial disease* the LV is greatly dilated with poor systolic function[61] Ventricular volumes are large the stroke volume is small and operative end diastolic pressure is high In myocarditis with acute LV dilatation LV chamber stiffness and presumably wall stress are high There is severe LV failure In chronic myocardial failure (congestive cardiomyopathy) *chamber stiffness* and its modulus (measured as a chord from early to end diastole) are slightly decreased perhaps again an adaptation to chronic volume loading[54]

The range of values is large an expected finding in this disease of uncertain etiology where we may be examining a heterogeneous population We found that operative end diastolic fiber stress is increased while Mirsky and associates [6] showed an increase in both elastic stiffness and k Peak negative dp/dt is decreased

Infiltrative cardiomyopathy (e g amyloidosis) is associated with a normal sized LV with relatively normal systolic function but stiff muscle presumably (high k) the LVEDP is increased [1]

Constrictive pericarditis In constrictive pericarditis pericardial fibrosis and/or calcification limits ventricular filling [1] Peak negative dp/dt is moderately reduced [35] the 0 point of the LV pressure pulse tracing is increased and rapid ventricular filling ends with a palpable and audible early diastolic filling halt (third heart sound) During slow ventricular filling there is little further change in LV pressure and volume and the a wave is relatively unimportant in most patients To make meaningful analysis of ventricular relaxation and filling in constrictive pericarditis diastole should be analyzed continuously since the relative contribution of myocardial and pericardial factors to over all chamber stiffness almost certainly changes in the different phases of diastole However most studies until now have measured over all diastolic function of the LV [17] The over all P–V curve (measured as a chord from the 0 point to end diastole) is shifted upwards and to the left Ventricular volumes are small while *chamber stiffness* and its modulus k_p are increased There have been no studies which measure LV wall stress and *stress–strain* relations Such studies should ideally examine the relative contributions of myocardium and thickened pericardium to total ventricular wall thickness and compliance

Effect of premature ventricular contractions There is no change in the modulus of chamber stiffness after the ectopic beat or after the post extrasystolic beat in normal man and in conscious dogs Increased filling during the post extrasystolic pause causes the ventricle to operate higher on the steep (stiffer) portion of its pressure–volume curve There is a preload dependent change in compliance without a change in stiffness modulus The diastolic properties of a failing ventricle with an increased EDP may differ though and earlier studies showed variable diastolic compliance after extrasystoles In these ventricles increased compliance was seen in the immediate post extrasystolic pause

Effect of drugs changes in preload and after load *Nitroglycerin* improves LV chamber compliance by reducing *preload* and *afterload* Ventricular volume decreases and end diastolic stress and pressure fall as the ventricle moves down its compliance curve (Fig 2) In addition (as with sodium nitroprusside) there is a downward shift in the entire pressure–volume curve without a change in its slope k_p The time course T of relaxation is not altered and it has been suggested that the change in the curve may be the result of a change in external constraints of LV filling such as decreased RV filling [56] The decrease in LV end diastolic pressure permits improved diastolic coronary filling there is improved myocardial oxygenation and this leads to further improvement in LV compliance as ischemia is relieved and muscle stiffness falls

Sodium nitroprusside decreases ventricular afterload and ventricular volume decreases (as a result of better systolic emptying) Sodium nitroprusside also affects the diastolic properties of the LV and there is a downward shift of the LV P–V curve so that for any given volume pressure is lower

Effect of beta adrenergic blocking drugs *Propranolol* has been found to increase end diastolic volume for a given end diastolic pressure (increased LV compliance) in patients with coronary artery disease and impaired systolic function [6] There was no difference however in the slope k_p of the log P volume curve in patients with CAD We do not have data relating to the effect of beta blockade on muscle stiffness in CAD

In hypertrophic cardiomyopathy (HOCM) *acebutolol* has been shown to decrease both beginning and end diastolic ventricular pressure at similar LV volumes again implying increased LV compliance but there was again no change in the modulus of chamber stiffness k_p [6] Calculation of k_p was less accurate in this study, however since pressure and volume were not recorded simultaneously and there are no data relating to muscle stiffness and k

Unanswered questions

Studies of diastole have provided a large amount of information about ventricular relaxation and filling but there are many unanswered questions Which is the primary step in the

cardiac relaxation process? What is the precise correlation between molecular and biochemical processes and events in the intact heart? What is the importance of plasticity and viscosity and the relation between static and dynamic compliance? The time course of relaxation requires extensive study as does a detailed analysis of instantaneous LV muscle and chamber function during each phase of diastole in different diseases. There is little detailed information relating to changes in ventricular muscle and chamber distensibility after medical or surgical intervention and little information relating to the prognostic significance of such changes.

The relation between the hemodynamic data and the clinical picture is interesting but not completely understood. Increased diastolic pressures cause left atrial and pulmonary venous hypertension with shortness of breath and in many patients an additional third and/or fourth heart sound. The precise setting for the genesis of a third or fourth heart sound in a given patient with decreased LV compliance is uncertain. A third heart sound is usually found in a large dilated left ventricle. It appears that ventricular filling is sufficient to produce the change of momentum required for a third heart sound at the end of the rapid filling phase in these patients since according to the Laplace relationship a large ventricle can distend fairly rapidly in the first third of diastole while the relative contribution of atrial systole later in diastole need be small or moderate. On the other hand a fourth heart sound is usually heard in a non-compliant ventricle of normal or decreased cavity size where atrial filling contributes a relatively large volume of blood to total ventricular filling. It is possible that a thick walled ventricle with small cavity size expands with difficulty in the first part of diastole and there is thus insufficient volume transfer and change of momentum during this period to produce the energy required for a third heart sound. The quantitative importance of the LV volume/mass ratio and the moduli of chamber and muscle stiffness in this regard are not certain. Studies of LV filling patterns in relation to other measurements of ventricular relaxation may supply more precise data as to the precise pathophysiological mechanisms underlying the genesis of third and fourth heart sounds in individual patients.

Finally the use of the term "cardiac failure and congestive heart failure" should now be reviewed. Traditionally these terms were used to describe patients with the physical signs of an elevated jugular venous pressure, hepatomegaly, edema, shortness of breath and chest rales. These are all signs of elevated *diastolic* filling pressures (right or left sided) and really indicate abnormal LV chamber compliance, the result of several possible mechanisms (Table I)—increased ventricular volume or an increased modulus of chamber stiffness due to hypertrophy and geometrical changes with or without additional changes in intrinsic muscle stiffness and k. In some patients with cardiac failure systolic ventricular function and cardiac output are normal or increased; in others cardiac output is low, the patients are cold, sweaty, have a low blood pressure and may be in a state of shock. The terms "low output failure" and "high output failure" were used to distinguish patients with a low cardiac output from those who maintained good or adequate systolic LV performance despite the signs of "congestive heart failure". High output failure occurs in conditions such as beri beri and anemia, where systolic muscle function is increased, normal or relatively normal despite the diastolic compliance abnormality. It seems then that at this time the clinical cardiologist should better describe the actual physical findings in a given patient and interpret these in terms of (1) abnormalities of systolic pump performance and (2) abnormalities of diastolic ventricular compliance. General terms such as "cardiac failure" or "congestive heart failure" are no longer adequate for the cardiologist to describe with accuracy the pathophysiological hemodynamic abnormalities in heart disease or to guide in their treatment.

REFERENCES

1. Spotnitz, H. M., and Sonnenblick, E. H.: Structural conditions in the hypertrophied and failing heart, *in* Congestive Heart Failure, D. T. Mason, ed., New York, 1976, Yorke Medical Books.
2. Schwartz, A.: Subcellular calcium transport mechanisms in the normal and failing heart, *in* Paul D. White Symposium in Cardiovascular Disease, H. L. Russek, ed., p 1[illegible], Baltimore, 1973, The Williams & Wilkins Co.
3. Huxley, A. F.: Muscle structure and theories of contraction, Progr Biophys 7:25[illegible], 195[illegible].
4. Huxley, A. F., and Simmons, R. M.: Proposed mechanism of force generation in striated muscle, Nature 233:5[illegible], 1971.
5. [illegible], M. I. M., and Pollack, G. H.: Molecular mechanism of contraction, Circ Res 40:333, 19[illegible].
6. Gordon, A. M., and Ridgway, E. B.: Calcium transient

and relaxation in single muscle fibers. Fourth Workshop on Contractile Behaviour of the Heart Utrecht The Netherlands 4 6 Sept 1977 Eur J Cardiol. 7(Suppl) 27 1978

7 Taylor S R and Rudel R Striated muscle fibers inactivation of contraction induced by shortening Science 167 882 1970

8 Brutsaert D L. De Clerck N M Goethals M A and Housmans P R Mechanisms of relaxation in isolated cardiac muscle Fourth Workshop on Contractile Behaviour of the Heart Utrecht The Netherlands, 4-6 Sept. 1977 Eur J Cardiol 7(Suppl) 71 1978

9 Nayler W G and Williams A J Relaxation in mammalian heart muscle some ultrastructural and biochemical considerations. Fourth Workshop on Contractile Behaviour of the Heart Utrecht The Netherlands 4 6 Sept 1977 Eur J Cardiol 7(Suppl) 35 1978

10 Morad M Inotropic effect of adrenaline on cardiac muscle does it relax or potentiate tension? Fourth Workshop on Contractile Behaviour of the Heart Utrecht, The Netherlands 4-6 Sept 1977 Eur J Cardiol. 7(Suppl.) 53 1978

11 Vassort G M., Roulet M J Mongo K. G., and Ventura Clapier R. F Control of the frog heart relaxation by Na Ca exchange Fourth Workshop on Contractile Behaviour of the Heart Utrecht The Netherlands 4-6 Sept 1977 Eur J Cardiol 7(Suppl.) 33 1978

12 Strobeck, J E and Krueger J W Influence of sarcomere motion on cardiac relaxation Fourth Workshop on Contractile Behaviour of the Heart Utrecht The Netherlands 4 6 Sept 1977 Eur J Cardiol 7(Suppl.) 79 1978

13 Winegrad S Robinson T and McClellan G Force transmission among cells in the relaxing heart Fourth Workshop on Contractile Behaviour of the Heart Utrecht The Netherlands 4-6 Sept 1977 Eur J Cardiol. 7(Suppl) 63 1978

14 Braunwald E and Ross J., Jr The ventricular end diastolic pressure Appraisal of its value in the recognition of ventricular failure in man Am. J Med 34 147 1963

15 Diamond G and Forrester J S Effect of coronary artery disease and acute myocardial infarction in left ventricular compliance in man Circulation 45 11 1972

16 Barry W H Brooker J Z., Alderman E L. and Harrison, D C Changes in diastolic stiffness and tone of the left ventricle during angina pectoris, Circulation 49 255 1974

17 Lewis B S and Gotsman, M S Left ventricular function in systole and diastole in constrictive pericarditis Am Heart J 86 23 1973

18 Gotsman M S and Lewis B S Left ventricular volumes and compliance in hypertrophic cardiomyopathy Chest 66 498 1974

19 Smith M Russell R O Field B J and Rackley C E Left ventricular compliance and abnormally contracting segments in post myocardial infarction patients, Chest 65 368 1974

20 Gaasch, W H., Battle W E., Oboler A A. Banas J S and Levine H J Left ventricular stress and compliance in man with special reference to normalized ventricular function curves Circulation 45 746 1972

21 Gaasch W H Levine H J Quinones, M A., and Alexander J K Left ventricular compliance mechanisms and clinical implications Am J Cardiol. 38 645 1976

22 Sonnenblick, E H Spiro D., and Spotnitz, H M The ultrastructural basis of Starling's law of the heart the role of the sarcomere in determining ventricular size and stroke volume Am Heart J 68 336 1964

23 Ross, J Jr Sonnenblick E H., Taylor R R Spotnitz H M., and Covell, J W Diastolic geometry and sarcomere lengths in the chronically dilated canine left ventricle Circ Res 28 49 1971

24 Taylor R R and Hopkins B E Left ventricular response to experimentally induced chronic aortic regurgitation Cardiovasc. Res 6 404 1972.

25 Tyberg J V., Glantz, S A., Misbach G Moores W Y., and Parmley W W Effects of altered loading ventricular interaction and the pericardium on left ventricular diastolic pressure dimension relation. Fourth Workshop on Contractile Behaviour of the Heart Utrecht The Netherlands, 4-6 Sept 1977 Eur J Cardiol. 7(Suppl) 163 1978

26 Mirsky I Cohn P R., Levine J A., Gorlin R Herman, M V., Kreulen T H and Sonnenblick E H Assessment of left ventricular stiffness in primary myocardial disease and coronary artery disease Circulation 50 128 1974

27 Mirsky I Assessment of passive elastic stiffness of cardiac muscle mathematical concepts, physiologic and clinical considerations, directions of future research, Progr Cardiovasc Dis. 28 277 1976

28 Parmley W W., Chuck, L., Kivowitz, C., Matloff J M., and Swan H J C In vitro length-tension relations of human ventricular aneurysms Relation of stiffness to mechanical advantage Am J Cardiol. 32 889 1973.

29 Gibson, D G., and Brown D J Relation between diastolic left ventricular wall stress and strain in man, Br Heart J 36 1066 1974

30 Moskowitz, S E., Lewis, B S Halon D A., Amar R., and Gotsman M S Computer prediction of left ventricular compliance throughout diastole in normal patients. Fourth Workshop on Contractile Behaviour of the heart 4-6 Sept 1977 Utrecht The Netherlands, Eur J Cardiol. 7(Suppl) 121 1978

31 Weisfeldt M L., Scully H E., Frederikson J., Rubenstein J J Pohost, G M., Beierholm E Bella A G., and Daggett, W M Hemodynamic determinants of maximum negative dP/dt and periods of diastole Am. J Physiol. 227 613 1974

32 Cohn P F., Liedtke A J., Serur J., Sonnenblick, E. H., and Urschel, C W Maximal rate of pressure fall (peak negative dP/dt) during ventricular relaxation Cardiovasc Res. 6 263 1972

33 Weiss J L., Frederikson J W., and Weisfeldt M L. Haemodynamic determinants of the time-course of fall in left ventricular pressure J Clin Invest 58 751 1976

34 McLaurin L. P., Rolett E L., and Grossman W Impaired left ventricular relaxation during pacing induced ischemia Am J Cardiol., 32 751 1973

35 Rickards, A., and Seabra Gomes, R Changes in regional diastolic function of the left ventricle following the induction of angina Fourth Workshop on Contractile Behaviour of the Heart Utrecht The Netherlands 4-6 Sept 1977 Eur J Cardiol 7(Suppl) 213 1978

36 Grossman W., and Tift Mann J Evidence for impaired myocardial relaxation during acute ischaemia in man. Fourth Workshop on Contractile Behaviour of the Heart. Utrecht The Netherlands 4-6 Sept 1977 Eur J Cardiol 7(Suppl.) 239 1978

37 Schwartz A Biochemical studies concerning etiology of hypertrophy heart failure and cardiomyopathy *in* Cardiomyopathies, vol. 2 of Recent Advances in Studies on Cardiac Structure and Metabolism p 501 E Bajusz and G Rona eds Baltimore 1973 University Park Press.

38 Lewis B S and Gotsman M S Maximal rate of fall of left ventricular pressure in cardiomyopathy and constrictive pericarditis S Afr Med J 49 1287 1975
39 Prewitt T Gibson D G Brown D and Sutton G The rapid filling wave of the apex cardiogram Its relation to echocardiographic and cineangiographic measurements of ventricular filling Br Heart J 37 1256 1975
40 Venco A St John Sutton M G., Gibson D G and Brown D J Non invasive assessment of left ventricular function after correction of severe aortic regurgitation Br Heart J 38 1324 1976
41 Sanderson J E Gibson D G Brown D J and Goodwin J F Left ventricular filling in hypertrophic cardiomyopathy An angiographic study Br Heart J 39 661 1977
42 Traill T A Gibson D G and Brown D J Study of left ventricular wall thickness and dimension changes using echocardiography Br Heart J 40 162 1978
43 Upton M T Gibson D G and Brown D J Echocardiographic assessment of abnormal left ventricular relaxation in man Br Heart J 38 1001 1976
44 Gibson D G Prewitt T A. and Brown D J Analysis of left ventricular wall movement during isovolumic relaxation and its relation to coronary artery disease Br Heart J 38 1010 1976
45 Krayenbuehl H P Turina J and Hess O Left ventricular function in chronic pulmonary hypertension Am J Cardiol 41 1150 1978
46 St John Sutton M G and Gibson D G Measurement of postoperative pericardial pressure in man Br Heart J 39 1 1977
47 Lewis C M Barnard P M van der Walt J J and Brink A J Haemodynamic basis for pericardiotomy as palliative treatment of idiopathic endomyocardiopathy *in* Cardiomyopathies vol 2 of Recent Advances in Cardiac Structure and Metabolism p 797 E Bajusz and G Rona eds Baltimore 1973 University Park Press
48 Falsetti H L. Mates R E Grant C Greene D G and Bunnell I L Left ventricular wall stress calculated from one plane cineangiography Circ Res 26 71 1970
49 Wong A Y K and Rautaharju P M Stress distribution within the left ventricular wall approximated as a thick ellipsoidal shell AM HEART J 57 649 1968
50 Hood W P Thomson W J Rackley C E and Rolett F L. Comparison of calculations of left ventricular wall stress in man from thin walled and thick walled ellipsoidal models Circ Res 24 575 1969
51 Mirsky I Ventricular stiffness Circ Res 34 123 1974
52 Pao Y C Ritman E L. and Wood E H Finite element analysis of left ventricular myocardial stresses J Biomechan 7 469 1974
53 Pao Y C and Ritman E L Global Young s modulus of urethane plastic cast of left ventricular myocardium calculated from angiographic silhouettes J Biomechan 10 133 1977
54 Lewis B S Mitha A S and Gotsman M S Left ventricular function in systole and diastole in aortic incompetence Isr J Med Sci 11 420 1975
55 Lewis B S., and Gotsman M S Left ventricular diastolic pressure-volume relations in man S Afr Med J 50 97 1976
56 Peterson K L., Tsuji J Johnson A DiDonna J and Le Winter M Diastolic left ventricular pressure volume and stress-strain relations in patient with valvular aortic stenosis and left ventricular hypertrophy Circulation 58 77 1978
57 Forrester J S Diamond G Parmley W W and Swan H J C Early increase in left ventricular compliance after myocardial infarction J Clin Invest 51 598 1972
58 Salisbury P F Cross C E and Rieben P A Influence of coronary artery pressure upon myocardial elasticity Circ Res 8 794 1960
59 Gaasch W H and Bernard S A The effect of acute changes in coronary blood flow on left ventricular end diastolic wall thickness an echocardiographic study Circulation 56 593 1977
60 Hood W B Bianco J A Kumar R and Whiting, R. B Experimental myocardial infarction IV Reduction of left ventricular compliance in the healing phase J Clin Invest 49 1316 1970
61 Gotsman M S Lewis B S Mitha A S and Bakst, A Left ventricular performance in congestive cardiomyopathy *in* Cardiomyopathies vol 2 of Recent Advances in Cardiac Structure and Metabolism E Bajusz and G Rona eds p 677 Baltimore 1973 University Park Press
62 Lewis B S and Gotsman M S Cardiac hypertrophy and left ventricular end diastolic stress Isr J Med Sci. 11 299 1975
63 Chew C Ziady G M Raphael M J and Oakley C M The functional defect in amyloid heart disease The stiff heart syndrome Am J Cardiol 36 438 1975
64 Gaasch W H Bing O H L Cole J S and Hanley H G Post extrasystolic compliance of the left ventricle Circulation 56 540 1977
65 Bartlestone H J Scherlag B J Hoffman B F and Cranefield P F Demonstration of variable diastolic compliance associated with paired stimulation of the dog heart Bull N Y Acad. Med 41 616 1965
66 Ludbrook P A Byrne J D Kurnik P B and McKnight R C Influence of reduction of preload and afterload by nitroglycerin on left ventricular diastolic pressure-volume relations and relaxation in man Circulation 56 937 1977
67 Brodie B R Grossman W Mann T and McLaurin L P Effects of sodium nitroprusside on left ventricular diastolic pressure-volume relations J Clin. Invest. 59 59 1977
68 Coltart D J Alderman E L Robison S C and Harrison D C Effect of propranolol on left ventricular function segmental wall motion and diastolic pressure-volume relation in man Br Heart J 37 35 1975
69 Lewis B S Mitha A S Bakst A Purdon K L and Gotsman M S Haemodynamic effects of beta blockade in hypertrophic cardiomyopathy using Sectral (M and B 17803A) Cardiovasc Res 8 249 1974
70 Kennish A Yellin E and Frater F W Dynamic stiffness profiles in the left ventricle J Appl. Physiol. 39 665 1975
71 Gaasch W H Cole J S Quinones M A and Alexander J K Dynamic determinants of left ventricular diastolic pressure-volume relations in man Circulation 57 317 1975
72 Rankin J S Aventzen C E McHale P A Ling D and Anderson R W Visco elastic properties of the diastolic left ventricle in the conscious dog Circ Res 41 37 1977
73 Gault J H Covell J W Braunwald F and Ross J Jr Left ventricular performance following correction of free aortic regurgitation Circulation 42 773 1970
74 Webb Peploe M M Croxson R S Oakley C M and Goodwin J F Cardioselective beta adrenergic blockade in hypertrophic obstructive cardiomyopathy Postgrad. Med J 47 93 1971

Fundamentals of clinical cardiology

Nitrate tolerance and dependence

Jonathan Abrams M D
Albuquerque N M

Nitroglycerin (NTG glyceryl trinitrate) and other organic nitrates are widely used in the care of patients with cardiovascular disease Long acting nitrates once viewed as ineffective by many investigators[1] are now accepted as physiologically active compounds that maintain their effect over many hours[4]

The problem of tolerance to organic nitrates has been raised since the first clinical reports of NTG therapy for hypertension in Bright s disease In 1888 Stewart reported a case of NTG tolerance in a man who required 20 grains of pure NTG to achieve the same hypotensive effect as the initial dose of 1/100 grain[5] He later stressed that this was a common problem in clinical practice[6] Many other workers including well known pharmacologists[7] [8] have subsequently cautioned physicians about the potential problem of NTG tolerance Prominent clinicians have continued to raise questions about nitrate tolerance and have left the issue unresolved[9] Others have strongly stated that tolerance is not an important clinical problem[1] A major source of concern has come from the explosives industry where a multitude of reports from 1898 to the 1960 s have unequivocally documented withdrawal symptoms in workers daily exposed to nitrate compounds who are temporarily away from the work environment[5] Although the munitions industry experience has been noted in the clinical literature Morton recently stated that nonoccupational physicians have taken too little heed of the industrial evidence regarding NTG tolerance and has recommended further study

Nitrate tolerance revisited

Until the mid 1970 s the question of nitrate tolerance in cardiovascular disease had been relatively unimportant The utilization of large amounts of sublingual NTG in patients with angina has rarely been noted to result in significant tolerance even in individuals using huge quantities (20 tablets or more) daily Long acting nitrates were considered to be ineffective by most clinicians and many prominent investigators were adamant in their view that these agents had no role in clinical medicine[1] [6]

The advent of propranolol therapy for angina rapidly followed by the widespread application of coronary bypass grafting seemed to further vitiate the potential usefulness of these agents Two related phenomena have dramatically changed the perspective on these drugs (1) There have been a considerable number of recent well conducted clinical investigations that convincingly document the efficacy of long acting nitrates in the treatment of angina pectoris[27] Studies have proved beyond reasonable doubt that these agents can provide prolonged chest pain relief for patients with angina Exercise tolerance ischemic ST response to exercise and frequency of sublingual NTG consumption are all improved with judicious utilization of long acting nitrates (2) The advent of vasodilator therapy for congestive heart failure has provided a valuable new arena for long acting nitrates and a large number of studies have proved that these agents have potent and prolonged physiologic effects[7] Vasodilator therapy presently plays an integral role in the therapy of moderately severe congestive heart failure Nitrate formulations that are currently in widespread use are listed in Table I

For these reasons the question of nitrate tolerance and dependence takes on a new urgency in 1980 Nitrates are being used in large numbers of patients with cardiac disease and have become

From the Division of Cardiology Department of Medicine University of New Mexico School of Medicine Albuquerque N M

Received for publication April _, 19 9

Reprint requests Jonathan Abrams M D Division of Cardiology University of New Mexico School of Medicine Albuquerque N M 87131

0002-8/03/80/010113 + 11$01 10/0 © 1980 The C V Mosby Co

Table I Clinically available nitrate drugs

Nitroglycerin (glyceryl trinitrate) formulations
Sublingual
Oral
Oral sustained action
Ointment
Synthetic organic nitrates
Isosorbide dinitrate
Oral
Oral sustained action
Sublingual
Chewable
Pentaerythritol tetranitrate
Oral
Oral sustained action
Erythrityl tetranitrate
Oral
Sublingual
Chewable

routine adjunctive therapy in heart failure.[1] There is increasing experience with high dose organic nitrate formulation. Isosorbide dinitrate (ISD) regimens of 20 to 40 mg three to four times a day or more have been given in a number of recent studies. Previous animal and human[3] data suggest that nitrate tolerance is more readily induced with large doses of nitrates. It is thus timely to reexamine the evidence for nitrate tolerance and dependence and to carefully evaluate recent clinical studies that deal with this problem.

Definitions

Tolerance to a drug exists when increasing dosage is required to obtain a given therapeutic effect.[16] It is a general phenomenon seen with a wide variety of agents particularly those affecting the central nervous system. The mechanisms underlying tolerance are poorly understood and may involve multiple complex and independent phenomena. It is common to acquire tolerance to some but not all of a drug's actions and to have varying degrees of tolerance with respect to different drug effects. Often drug activity is of shortened duration and lesser intensity in the tolerant subject. The requisite lethal dose may increase enormously. Tolerance classically disappears after cessation of drug therapy and develops again after an appropriate period following reinstitution of the drug.

Cross tolerance often occurs with related compounds and implies that more than one agent can induce tolerance to a given drug. A single drug may produce tolerance to other similar drugs.

Dependence on a drug means that psychic and/or physical symptoms will appear when the substance is discontinued.[16] *Withdrawal syndromes* are typical of various mood and behavior altering drugs including alcohol, opiates, amphetamines, and sedative hypnotics. Frequently there is a rebound effect with apparent increased "susceptibility" of physiologic systems affected by the compound. There can be *cross dependence* among related drugs. Although tolerance and physical dependence commonly occur together, one may exist without the other.[3] This is important to keep in mind when considering nitrate effects: both tolerance and dependence may be implicated in some subjects but either phenomenon can be an isolated problem in others.

Evidence supporting nitrate tolerance and dependence

Clinical experience NTG was initially used for the treatment of hypertension. Mild to severe headaches are commonly encountered; these often disappear with continued drug treatment. Countless reports have documented this sequence including many contemporary studies. This strongly suggests the development of acquired tolerance to the cerebral vasodilator actions of NTG. Other nitrate side effects such as dizziness and nausea may also abate after several days of therapy. This phenomenon is also true for organic nitrates such as ISD: headaches are common early in therapy but tend to disappear with continued therapy.

There are anecdotal reports of patients who lose their clinical response to NTG and require increased NTG dosage. These cases are quite uncommon and find scant documentation in the literature.

Munitions industry experience The most impressive evidence for nitrate tolerance and dependence comes from the industrial experience in explosives manufacturing plants. NTG and ethylene glycol dinitrate (nitroglycol) are fundamental components of dynamite and other explosives. These agents are strongly implicated in a whole array of medical problems seen in factory workers exposed to these agents. A characteristic syndrome has been recognized since 1898.[19] The

consists of the occurrence of mild to severe headaches ("powder headaches") in exposed workers at the end of weekend breaks or other layoffs from work. Characteristically, the headaches begin Sunday or early Monday morning approximately 48 to 72 hours after the employee is absent from the nitrate laden environment. Workers are known to rub NTG into their skin or use impregnated headbands on weekends to avoid these headaches; some take medicinal NTG for this purpose. Studies of munitions factory employees have demonstrated decreased systolic blood pressure, decreased pulse pressure, increased heart rate, and abnormal finger pulse wave contours. These abnormalities completely disappear when the worker is removed from nitrate exposure for 24 to 72 hours. Similar experiences have been documented in pharmaceutical NTG workers.[1] Isolated reports of these problems appeared in the European literature[3] and less often in the United States in industrial medicine publications.

Widespread medical awareness of the risks of industrial nitrate exposure in this country followed the report of Lange and associates in 1972 when vastly more serious sequelae of dynamite manufacturing were reported, i.e., chest pain and sudden death. Europeans had described this phenomenon years earlier. In 1952 a German report first documented three cases of sudden death among nitroglycol workers.[4] These authors surveyed the world industrial experience and turned up 44 other deaths, 37 from the United States. Other similar reports appeared in the European literature. The first United States report came in 1963 following a careful investigation into a number of deaths occurring in several Pennsylvania dynamite plants. This excellent paper was ignored by clinicians and in fact a review of the toxicity of NTG in 1965 failed to cite either the European or United States experience of nitrate related chest pain syndromes and sudden death.

Characteristically, exposed workers complain of nonexertional substernal chest pressure or pain on the Sunday or Monday following a weekend break from work. The pains may be mild or severe. A number of deaths as well as acute myocardial infarctions have been documented. It has been postulated that withdrawal from nitroglycerin or nitroglycol results in unopposed (? reflex) coronary and systemic vasoconstriction with subsequent coronary ischemia;[1] elevated diastolic blood pressures and lowered systolic and pulse pressures in exposed workers lend credence to the theory of rebound vasoconstriction. Of great importance was the documentation by coronary arteriography of normal coronary arteries in four such individuals and coronary vasospasm in one with recurrent chest pain.[1] More recently, Klock also documented coronary vasospasm with normal vessels in a young male dynamite worker with severe chest pain occurring when he was unexposed to the work environment. Workers who have chest pain syndromes generally become permanently free of symptoms upon long term removal from nitrate exposure.

These cases all support the concept that withdrawal coronary vasospasm does occur in some munitions workers who are chronically exposed to nitrates. This dependence poses an enormous health hazard. Industrial hygiene and public safety groups have recommended strict criteria for protection of munitions workers.[3] It has been well established that both NTG and nitroglycol penetrate clothing and protective gloves, and rigorous techniques are necessary to prevent cutaneous absorption of the offending substances. Nitroglycol is also present in vapor form in the ambient air and can be absorbed through the respiratory system. Both substances are present in explosives manufacturing and it is unclear whether one or both are responsible for the various withdrawal syndromes. Klock,[4] Carmichael and Lieben,[1] and others[5] have even suggested that chronic NTG exposure may lead to accelerated atherosclerosis in these workers. Hueper and Landsberg[5] produced degenerative vascular lesions in young rats by chronic nitrite and nitrate exposure and believe this may explain the atherosclerosis seen in chronic nitrite poisoning. They postulated that protracted vasodilatation interferes with normal coronary artery nutrient blood supply and results in vascular injury. This theory seems unlikely and requires more research before any firm conclusions can be drawn. The evidence that munitions workers do in fact have increased atherosclerosis is only anecdotal.

It is thus indisputably clear that chronic exposure to high concentrations of NTG or organic nitrates can result in tolerance (disappearance of headaches after several days of work) and de

pendence (Monday syndrome chest pain myocardial infarction) Whether this unusual industrial hazard has any relevance to patients given far smaller and much more intermittent exposure to nitrates is certainly debatable

Animal studies Tolerance to NTG has been readily produced in rats rabbits and dogs and the degree of tolerance is directly related to the size of the dose administered Decreased responsiveness to nitrates rapidly develops and when massive amounts of NTG are used vascular smooth muscle may become totally insensitive to repeat nitrate administration Even a single dose of NTG in rats can produce some tolerance Tolerance rapidly disappears after cessation of nitrate administration Experiments by Needleman and Johnson and Needleman have excluded decreased availability of free drug tissue exhaustion increased biotransformation or increased sympathetic activity as mechanisms for tolerance In a subsequent discussion Needleman and Johnson proposed that the cellular mechanism of tolerance to NTG is a result of nitrate induced oxidation of sulfhydryl groups in vascular smooth muscle nitrate receptor sites organic nitrates act at these receptors to produce vascular relaxation The disulfide receptor has less affinity for NTG In animals made tolerant to NTG they were able to reverse the in vitro loss of nitrate sensitivity by exposing the vascular wall to a disulfide reducing agent thus returning vessel reactivity to normal Cross tolerance was easily produced to NTG by a group of organic nitrates Cohen and Kirk recently demonstrated small coronary artery tachyphylaxis to continuous intravenous NTG in ischemic dog hearts while the proximal large coronary arteries continued to be responsive to the nitrate The clinical significance of this observation is far from clear this experimental model was not designed to evaluate the overall problem of tolerance

Human studies Almost 50 years ago Crandall and co workers investigated tolerance in normal volunteers because of clinical experience suggesting tolerance to nitrates was a common problem in the treatment of hypertension and was an obstacle to successful therapeutic use They examined tolerance by assessing the headache dose as well as blood pressure and heart rate changes induced by various nitrates Virtually complete cross tolerance was readily produced among a group of organic nitrates including NTG Of interest they noted that tolerance to headache producing action is more easily established than is tolerance to effects on blood pressure and pulse rate

In 1955 Bernstein and Ivy easily produced tolerance to two long acting nitrates in hypertensive patients This occurred in 8 to 14 days and disappeared within weeks of cessation of nitrate therapy Cross tolerance was observed to sublingual NTG used for relief of chest pain in some of these patients who had angina More recently Schelling and Lasagna documented decreased responsiveness to headache and blood pressure-heart rate changes induced by NTG in a group of subjects treated with pentaerythritol tetranitrate (PET) for 4 weeks This often cited study showed that only partial tolerance was induced by PET the response to sublingual NTG was attenuated somewhat but not obliterated. These authors called for improved physician education and further study about the problem of nitrate tolerance

In order to address the question of cross tolerance to NTG induced by long acting nitrates Zelis Mason and co workers studied arterial and venous vascular tone and blood flow in six normal subjects given large doses of ISD Sublingual NTG resulted in decreased calf vascular resistance and increased calf blood flow as well as an increase in forearm venous volume Following 6 to 8 weeks of treatment with 120 mg oral ISD daily there was no loss of the arteriolar response to NTG following sublingual administration of NTG calf vascular resistance and mean arterial pressure fell to the same extent as the pre ISD measurements Equivalent vascular responsiveness was also seen after alpha adrenergic blockage and sodium nitrate administration intra arterially However the modest increase (9%) in forearm venous volume produced by NTG was totally blunted after chronic ISD treatment They concluded that tolerance to venous reactivity induced by ISD readily occurs in the absence of any tolerance to the arteriolar actions of NTG It should be noted that the venous volume changes in the control state were relatively small. Nevertheless this study is potentially relevant to the use of vasodilator therapy for congestive heart failure The authors noted that ISD induced headaches disappeared by the fourteenth day again demonstrating the dissociation between the different manifestations of nitrate tolerance

Summary The experience from industrial

exposure to organic nitrates ("Monday head ache," chest pain, sudden death), animal studies, and data obtained from a variety of clinical investigations into tolerance gives credence to the claim of many clinicians and pharmacologists that the development of nitrate tolerance is a potential hazard in patients chronically treated with long acting nitrates. Most of the documentation of nitrate tolerance in *individual patients*, however, is anecdotal and provides the weakest link in the argument for tolerance.

Evidence that nitrate tolerance and dependence are not major clinical problems

Clinical experience. While many reviews of nitrate therapy caution physicians about possible tolerance, they do not provide adequate documentation that this is a valid problem in everyday clinical practice. Experienced clinicians rarely identify patients who develop tolerance to the benefits of nitrate therapy. The disappearance of NTG headaches is, of course, an aspect of tolerance that is favorable. Established investigators in the nitrate field virtually never see patients who lose sensitivity to the desired effects of nitrates.[4] A possible case of nitrate dependence was recently reported in a man with severe Prinzmetal's angina and recurrent refractory coronary vasospasm.[5] The patient demonstrated no clinical response to ISD and NTG ointment but had a dramatic reduction in chest pain frequency with the addition of nifedipine, a potent experimental coronary vasodilator. He suffered an acute anteroseptal myocardial infarction 36 hours after withdrawal of long acting nitrates in the hospital. The authors concluded "it seems unlikely that nitrate withdrawal caused a rebound phenomenon since the duration of exposure was far shorter than that of individuals in whom infarction has been reported secondary to withdrawal from industrial exposure to NTG." They speculate that the nitrate withdrawal simply unmasked the intense coronary vasospasm in this patient. It is of interest that the nitrate therapy had been ineffective prior to institution of nifedipine. No definite conclusions regarding NTG dependence can be made from this unusual case.

There are patients with classic angina pectoris who require increasing NTG dosage and/or experience a loss of effectiveness of sublingual NTG.[3] This is generally considered to be accelerating or unstable angina. It is possible that some of these patients may actually have developed significant nitrate tolerance. There is, however, no present evidence to support this view. In a recent editorial, Zelis and associates state: "Despite decades of acceptance of the reality of nitrate tolerance and despite a firm scientific basis, many seasoned clinicians have had a nagging suspicion that this might be a highly overrated phenomenon." "The fear of clinically meaningful nitrate tolerance appears to be unfounded."

Studies using long acting nitrates in ambulatory patients with angina pectoris. Many studies have demonstrated long term efficacy of various nitrate formulations in angina utilizing chest pain frequency and NTG tablet counts. This type of "soft" data is not ideal to evaluate antianginal therapy; studies producing more valid data utilize serial exercise tests with appropriate controls (placebo groups, crossover trials, etc.).[5]

Three recent studies have demonstrated long term angina improvement in patients taking *oral* NTG.[7] Using a complex protocol, Winsor and Berger[7] concluded that "nitrate tachyphylaxis does not occur." According to diary notes and tablet counts over a 24 week period, the frequency and severity of angina attacks were significantly decreased in a group of patients taking active oral NTG versus placebo. Possible tolerance was investigated by carefully evaluating the weekly clinical status in patients with angina; none showed a decreased NTG effect over any 8 week period of oral NTG therapy. Serial exercise tests were not performed, but treadmill testing revealed improved performance with oral NTG after only 6 to 10 days of therapy. Cole and Kaye[9] documented protracted (6 month) angina protection using the diary method. Using a serial exercise test protocol, Davidov and Mroczek[10] repeated treadmill tests at 12 weeks and demonstrated sustained improvement in patients taking sustained action NTG versus placebo orally. Angina frequency was also decreased at 12 weeks in the active drug group.

NTG *ointment* has also been found to produce sustained relief of angina with no evidence of tolerance to sublingual or topical NTG after 8 to 12 weeks of therapy.[6] NTG ointment caused similar blood pressure and heart rate changes before and after chronic administration *and most important*, repeat challenge with sublingual NTG resulted in identical improvement as well as similar blood pressure and heart rate *response*. Nevertheless, the authors stated that

study is necessary to fully evaluate the problem of tolerance and dependence in patients given physiologically active nitrate formulations. *ISD* has been given chronically in several studies; tolerance has not been documented. In 1971 the NIH group showed that long-term treatment (1 to 7 months) with sublingual ISD (5 to 10 mg q.i.d.) did not attenuate the acute blood pressure, heart rate, or exercise test responses to readministered ISD. While questioning whether ISD had truly sustained activity when compared with NTG, these workers have repeatedly stated that tachyphylaxis and dependence is not a problem with the usual therapeutic doses of nitrates.

Recently an investigation of high-dose oral ISD using serial exercise tests was reported. Patients were studied with active ISD (40 mg t.i.d.) or placebo before and after 30 days of therapy. ISD resulted in sustained improvement in exercise tolerance and ST depression at 2 and 6 hours after dosing, and patients taking active drug showed a significant decreased frequency of angina attacks and NTG tablet use over the 30 day period. This study clearly demonstrates important physiologic responses to nitrates persisting for at least 30 days of therapy with no evidence of tolerance.

Studies using long-acting nitrates for congestive heart failure. The utilization of long-acting nitrates in the treatment of heart failure has provided further evidence that clinical tolerance to these agents is uncommon. More and more studies are currently being reported assessing the efficacy of unloading therapy in ambulatory patients with heart failure, often with higher doses of nitrates than have been used previously. Therefore further evidence regarding this potential problem will be forthcoming. Some preliminary data are already available.

In 1974 Cohn and co-workers reported a case of severe postinfarction heart failure in which only nitroprusside could reverse the deteriorating course. The patient was subsequently given oral ISD and NTG ointment which lowered the left ventricular filling pressure (LVFP). He was discharged on large doses of these drugs and had repeat catheterization 10 weeks later which documented appropriate responsiveness to sublingual NTG. Subsequent challenge with placebo instead of ISD resulted in exacerbation of congestive heart failure. After 8 months of chronic nitrate therapy the patient had a smaller heart size and continued to sustain clinical improvement. These authors treated seven similar ambulatory patients with severe left ventricular failure who "reported improvement in symptoms on vasodilator therapy." No evidence of tolerance was observed. Gray and associates[*] followed nine patients with chronic congestive heart failure on sublingual ISD (5 to 15 mg Q.I.D.) for 4 to 8 months. All had initially demonstrated acute responses to the drug while in the hospital; cardiac index and venous capacitance increased, while systemic resistance, pulmonary wedge pressure, and mean arterial pressure decreased. One patient had follow-up hemodynamic evaluation after 2 months of ISD administered on an outpatient basis; further improvement was demonstrated in most parameters. All patients were judged clinically to be improved. They recommended the use of sublingual ISD in the therapy of chronic heart failure. Kovick and associates[**] followed 12 patients with severe congestive heart failure (CHF) on chronic sublingual ISD and oral phenoxybenzamine for a mean of [illegible] months (range 3 to 21 months). Nine had repeat hemodynamic studies documenting continued improvement in cardiac output, fall in LVFP as well as a reduction in echo-derived left ventricular diastolic diameters. At repeat catheterization the patients were given sublingual ISD. Each showed a further reduction in PAW [pulmonary artery wedge pressure] and increase in CI [cardiac index] suggesting that tolerance to the nitrates had not developed. All were clinically improved, often with a dramatic decrease in diuretic requirements. Massie and associates used a combination of hydralazine and ISD in six ambulatory patients with severe CHF followed for a mean of 6 months (range 3 to 10 months); one additional patient was given NTG ointment. All seven have shown significant clinical improvement that has persisted for the duration of follow-up. Functional class improved in all. One subject was restudied at 8 months and was found to have maintained the vasodilator-induced hemodynamic improvement first documented when unloading therapy was instituted during the initial hospitalization. While hydralazine was partially beneficial in these patients, the nitrate therapy clearly was able to reduce LVFP; the follow-up data do not support the appearance of nitrate tolerance. In a subsequent discussion of these patients the authors comment, "admittedly further studies will be required to document that the hemodynamic effects of these drugs

continue to manifest with their continued use.[""] Addressing the problem of outpatient use of nitrates in congestive failure they state "Tolerance to various pharmacologic effects, however may be troublesome during the long term administration of NTG or the other nitrates It is apparent within a few days and may become of considerable magnitude within two weeks Fortunately tolerance appears to develop somewhat more readily to nitrate induced headaches than to other pharmacologic effects. This note of caution apparently was not based on any negative clinical experience

Chandraratna and associates[64] recently reported seven patients with severe biventricular congestive heart failure treated with NTG ointment after first documenting efficacy in the hospital with hemodynamic studies These patients had considerable clinical improvement at a mean 5-month follow up (range 2 to 12 months) several returning to functional Class I or II The initial nitrate headaches disappeared or decreased within a few days in all Follow up hemodynamic measurements were not made Another report using hydralazine and NTG ointment followed eight Class IV CHF patients for a mean of 5 months after the initial hemodynamic study All subjects showed subjective improvement with increased exercise capacity Most had a reduction in cardiac dimensions and a decrease in edema Functional class improved in all. Less dramatic results were seen in a series of nine left ventricular failure patients followed for a mean of 6 months (range 1 to 14 months) who received high dose chewable ISD plus hydralazine.[5] The regimen was well tolerated but objective evidence for improvement was limited Tolerance was not recognized The same group more recently reported the first controlled trial of chronic unloading therapy in CHF[73] Sixteen patients were randomized to ISD (40 mg orally q.i.d.) or placebo in a double blind 16-week crossover study Only six patients were able to complete the entire protocol. The nitrate group had significantly less "complicating events (7/85 versus 17/76) and most were clearly benefited when compared to the placebo group No patient deteriorated on ISD while the condition of five placebo treated patients worsened Exercise tolerance increased in the ISD group but half the placebo group also showed improved exercise performance Other objective evidence for improvement (physical examination chest x ray echo dimensions cardiac output) were no different in the ISD or placebo groups The authors conclude that nitrate therapy resulted in symptomatic clinical improvement but long term prognosis could not be assessed They did not find evidence of ISD tolerance However the possibility of nitrate dependence was raised in this study because of the disturbing number of clinical events (including two sudden deaths) in those patients with underlying ischemic heart disease who had been taking ISD prior to study and then discontinued the drug during the 4 week placebo run in period. Most "events" were worsening heart failure but the two deaths suggest a possible nitrate withdrawal effect similar to that seen in industrial workers exposed to NTG Most of these patients had been taking nitrates for less than 2 weeks and the numbers are small Thus further study of the possibility of nitrate dependence in this type of patient seems warranted

Studies designed to evaluate nitrate tolerance Aronow and Chesluk treated patients with angina for 4 weeks with sublingual ISD and then assessed their response to sublingual NTG Exercise improvement was seen following sublingual NTG administration in the subjects taking ISD or placebo with no suggestion of ISD induced attenuation to the NTG As already cited workers at the National Institutes of Health evaluated nitrate tolerance in patients receiving chronic ISD as well as topical NTG and found no loss of responsiveness to sublingual NTG or to the long acting nitrate that had been given for the duration of the study In the ISD study the response to acute ISD and sublingual NTG was evaluated by treadmill testing after 10 days of ISD in six patients and 1 to 7 months in another four patients Six subjects using NTG ointment were retested after 6 to 8 weeks of chronic therapy A patient was reported in 1971 who had taken oral ISD for 4 months and showed no tachyphylaxis to the drug's effect on improving exercise tolerance In a study measuring digital pneumoplethysmographic responses to nitrates it was shown that 1 week of treatment with oral sustained release NTG (5 mg b.i.d) did not alter the mean group response to the drug The methodology and statistical analysis in this study leave much to be desired

Two well-designed studies to evaluate the problem of tolerance and cross tolerance to high-dose ISD in patients with stable angina pectoris were recently reported Danahy and Aronow

followed 19 patients on oral ISD for 3 to 10 months The dose of ISD ranged from 10 to 50 mg q i d (average dose 27 mg) Responses to sublingual NTG and oral ISD were assessed by measurements of blood pressure heart rate and bicycle exercise performance up to 5 hours and were compared with similar measurements made prior to chronic nitrate treatment The improvement in exercise tolerance with NTG and ISD was similar during both evaluations Oral ISD produced sustained improvement in exercise performance at 1 and 3 hours but not at 5 hours before and after chronic use of the drug The ST segment responses to exercise were unchanged after ISD treatment Patients reported no decrease in the therapeutic benefit from sublingual NTG while taking high dose ISD However blood pressure and heart rate responses to ISD were attenuated after chronic treatment with this drug The mean decrease in systolic blood pressure and increase in heart rate on the post ISD treatment evaluation were less than pre ISD therapy the mean group responses were decreased at all testing periods up to 5 hours after oral ISD Thus the hemodynamic responses to an acute challenge with oral ISD were blunted as measured by blood pressure and heart rate but the antianginal efficacy of both sublingual NTG and oral ISD were unaltered following long term ISD administration This clearly suggests differential tolerance the various nitrate actions as has been noted in her studies Headaches induced by ISD were common but were absent or less severe in most subjects after 2 to 3 weeks of therapy again indicating partial ISD tolerance The discrepancy between the clinical and hemodynamic effects of chronic ISD was unaccounted for and the authors concluded We could detect no evidence of development of tolerance to the antianginal effect of the drug Similarly sublingual NTG remains effective after chronic use of ISD

In another similar study to investigate the problem of cross tolerance to ISD 28 patients with stable angina pectoris were given high dose oral ISD (120 mg daily) for a month [3] Peak exercise performance was measured as well as the exercise response to acute sublingual NTG administration The patients were able to respond maximally to sublingual NTG after chronic ISD treatment and showed increases in exercise duration and maximal oxygen consumption equivalent to the pre ISD measurements The ISD group also demonstrated greater pre NTG exercise capability than prior to the 4 weeks of treatment Exercise induced ST depression decreased in the ISD group administration of sublingual NTG produced no further reduction in the ischemic EKG response The data strongly suggest that tolerance to ISD itself did not develop Although the actual magnitude of NTG induced exercise improvement was less than in the placebo group following 1 month of ISD administration the authors emphasize that the ISD treated patients had already showed objective improvement prior to the administration of sublingual NTG and the maximal response following NTG was similar to that before treatment They conclude cross tolerance to the antianginal effect of sublingually administered NTG is not induced by long term oral administration of ISD

The most recent report available is that of Franciosa and Cohn[7] who used high-dose oral ISD (160 mg daily) for vasodilator therapy in CHF In a study designed to examine the possibility of tolerance they reevaluated 11 patients with right heart catheterization after 3 months of treatment with ISD or placebo The nitrate group showed a slightly lower baseline LVFP and continued to lower this pressure 90 minutes after acute ISD administration mean arterial pressure also fell in the ISD treated patients This study demonstrated sustained hemodynamic reactivity to the nitrate after prolonged high dose ISD therapy and does not support the appearance of ISD induced tolerance

Conclusions

1 There is little evidence that chronic administration of organic nitrates even in large doses induces clinically important tolerance or cross tolerance to NTG or other nitrates in patients being treated for angina pectoris or heart failure Recent well designed studies demonstrate the persistence of undiminished therapeutic activity in response to nitrate administration in patients treated with long acting nitrates for periods of 1 to 10 months Some attenuation of venous and arterial vasodilation following long term ISD therapy has been noted and is of uncertain clinical significance The experience from the explosives and NTG manufacturing industries as well as the results of a number of earlier animal and human studies clearly demonstrate that nitrate *tolerance and cross tolerance can occur* and often with dramatic speed Thus the *possibility* of

clinical tolerance must be kept in mind in the treatment of patients with long term nitrate therapy

2 Nitrate therapy for angina or heart failure should be judiciously initiated and thoughtfully maintained The lowest effective dosage should be utilized individual sensitivity to nitrate action is highly variable and totally unpredictable Because the experience with high dose nitrate administration is relatively new evidence for tolerance should be especially sought in patients receiving such therapy and periodic reassessment of the nitrate s efficacy should be made Earlier investigations suggest that nitrate tolerance is more likely and more quickly induced with high doses

3 The most serious problem of nitrate dependence is as yet unresolved Death myocardial infarction and chest pain syndromes have been amply documented in industrial employees exposed to NTG and nitroglycol who leave the work environment for several days Coronary spasm has been shown to occur in some of these individuals The recent report of Franciosa and co workers[74] again raises the specter of nitrate dependence but the patient population is too small and the experience too limited to draw any firm conclusions Although unlikely withdrawal syndromes may become a real clinical problem particularly in patients treated with high doses of nitrates similar reports have been recently described in propranolol therapy for angina pectoris many years after beta blockers were introduced for angina It seems prudent to carefully taper nitrate therapy in patients with proven coronary atherosclerosis who have been on chronic long acting nitrate regimens if the drug must be stopped These patients should be admonished to watch for symptoms of increased chest pain during the withdrawal period or when they discontinue their medication inadvertently The majority of studies reviewed in this report were designed to examine tolerance rather than dependence Further experience is necessary before the question of nitrate dependence can be fully answered

REFERENCES

1 Modell W Clinical pharmacology of antianginal drugs Clin Pharmacol 3 97 1962

2 Aronow W S and Chesluk H M Sublingual isosorbide dinitrate therapy versus sublingual placebo in angina pectoris Circulation 42 869 1970

3 Needleman P Efficacy of long acting nitrates Am J Cardiol 390 400 1976

4 Abrams, J Usefulness of long acting nitrates in cardiovascular disease Am J Med 64 183 1978

5 Stewart D D Remarkable tolerance to nitroglycer in 1888 Philadelphia Polyclinic p 172

6 Stewart D D Tolerance to nitroglycerin J.A M.A 44 16 8 1904

7 Nickerson M Vasodilator drugs, in Goodman, L S and Gilman A editors The Pharmacological Basis of Therapeutics, ed 5 New York 1975 Macmillan Publishing Co Inc p 732

8 Schelling J and Lasagna L A study of cross tolerance to circulatory effects of organic nitrates Clin Pharmacol Ther 8 256 1967

9 Fisch S Antianginal drugs II Human pharmacology of nitroglycerin AM HEART J 71 417 1966

10 Aronow W S Use of nitrates as antianginal agents in Needleman P editor Handbook of Experimental Pharmacology New York 1975 Springer Verlag New York Inc., vol 40 p 171

11 Kupersmith J Oral nitrate therapy in coronary artery disease Angiology 28 411 1977

12 Glancy D L Richter M A Ellis E V., and Johnson W Effect of swallowed isosorbide dinitrate on blood pressure heart rate and exercise capacity in patients with coronary artery disease Am J Med 62 39 1977

12a Aronow W S Clinical use of nitrates I Nitrates as antianginal drugs Mod Concepts Cardiovasc Dis. 48 31 1979

13 Reicheck N Long acting nitrates in the treatment of angina pectoris, J.A M.A 236 1399 1976

14 Zelis R Flaim S F Moskowitz R M., and Nellis S H How much can we expect from vasodilator therapy in congestive heart failure? Circulation 59 1092 1979

15 Laws, G C The effects of nitroglycerin upon those who manufacture it J.A M.A 31 793, 1898

16 Laws C E Nitroglycerin head J.A M.A 54 793 1910

17 Bright G E The effects of nitroglycerin on those engaged in its manufacture J A.M A 62 201 1914

18 Rabinowitch I M Acute nitroglycerin poisoning Can Med Assoc J 50 199 1944

19 Schwartz, A. M The cause relief and prevention of headaches arising from contact with dynamite N Engl J Med 235 651 1946

20 Einert C Adams W Crothers, R Moore H., and Ottoboni, F Exposure to mixtures of nitroglycerine and ethylene glycol dinitrate Am Ind Hyg Assoc J 24 435 1963

21 Carmichael P., and Lieben J Sudden death in explosives workers Arch Environ Health 7 50 1963

22. Morikawa Y Muraki K Ikoma Y., Honda T and Takamatsu H Organic nitrate poisoning at an explosives factory Arch Environ Health 14 614 1967

23 Lund R P., Haggendahl J and Johnsson G Withdrawal symptoms in workers exposed to nitroglycerine Br J Ind Med 25 136 1968

24 Morton W E Occupational habituation to aliphatic nitrates and the withdrawal hazards of coronary disease and hypertension J Occup Med 19 197 1977

25 Morton W E Personal communication 1978

26 Epstein S E Redwood D S Goldstein R E., and Fox L R Angina pectoris Pathophysiology evaluation and treatment Ann Intern Med 75 [illegible] 1971

27 Abrams J Current status of long [illegible] clinical medicine Pract Cardiol 3 17

28 Chatterjee K Massie B Rubin S Gelberg H Brundage B H and Forts T A Long term outpatient vasodilator therapy of congestive heart failure Consideration of agents at rest and during exercise Am J Med 65 134 1978
29 Franciosa S A Nordstrom L A, and Cohn J N Nitrate therapy for congestive heart failure J A M A 240 443 1978
30 Pierpont L L Cohn J N and Franciosa J A Combined oral hydralazine nitrate therapy in left ventricular failure Chest 73 8 1978
31 Shane S J High dose oral isosorbide dinitrate and ischaemic heart pain Can Fam Phys 19 61 1973
32 Shane S J Iazzetta J J Chisolm A W Berka J F and Leung D Plasma concentrations of isosorbide dinitrate and its metabolites after chronic high oral dosage in man Br J Clin Pharmacol 6 37 1978
33 Needleman P and Johnson E M Mechanism of tolerance development to organic nitrates J Pharmacol Exp Ther 184 709 1973
33a Needleman P and Johnson E M The pharmacological and biochemical interaction of organic nitrates with sulfhydryls Possible correlations with the mechanism for tolerance development vasodilation and mitochondrial and enzyme reactions in Needleman P editor Handbook of Experimental Pharmacology New York 1975 Springer Verlag New York Inc vol 40 p 97
34 Crandall L A Leake C D Loevenhart A S and Muehlberger C W Acquired tolerance to and cross tolerance between the nitrous and nitric acid esters and sodium nitrite in man J Pharmacol Exp Ther 41 103 1931
35 Bernstein L M and Ivy A C Inositol and mannitol hexanitrates in hypertension management Circulation 12 353 1955
36 Fingl E and Woodbury D M General principles, in Goodman L S and Gilman A editors The Pharmacological Basis of Therapeutics, ed 5 New York 1975 Macmillan Publishing Co Inc p 31
37 Jaffee J H Drug addiction and drug abuse in Goodman L S and Gilman A editors The pharmacological basis of therapeutics ed 5 New York 1975 Macmillan Publishing Co Inc P 286
38 Horwitz L D Herman M V and Gorlin R Clinical response to nitroglycerin as a diagnostic test for coronary artery disease Am J Cardiol 29 149 1972
39 Bresler R R Nitroglycerine reactions among pharmaceutical workers Industrial Med Surg 18 519 1949
40 Symanski H Schwere gesundheitsschädigungen durch berufliche nitroglykoleinwirkung Arch Hyg Bakt 136 139 1952
41 Barsotti M Attacchi stenocardici nei lavoratori addetti alla produzione delle dinamiti con nitroglicole Med Lavoro 45 544 1954
42 Munch J C Friedland B and Shepard M Glyceryl trinitrate II Chronic toxicity Industrial Med Surg 34 940 1965
43 Lange R L Reid M S Tresch D D Keelan M H Bernhard V M and Colledge G Nonatheromatous ischemic heart disease following withdrawal from chronic industrial nitroglycerin exposure Circulation 46 666 1972
44 Klock J C Non occlusive coronary disease after chronic exposure to nitrates Evidence for physiologic nitrate dependence Am Heart J 89 510 1975
45 Hueper W C and Landsberg J W Pathologic changes in the organs of rats produced by chronic nitrite poisoning Arch Pathol 29 633 1940
46 Bogaert M A Tolerance towards glyceryl trinitrate (trinitrin) in rabbits Arch Int Pharmacodyn 172 228 1968
47 Crandall L S The fate of glyceryl trinitrate in the tolerant and non tolerant animal J Pharmacol Exp Ther 48 127 1933
48 Needleman P Tolerance to the vascular effects of glyceryl trinitrate J Pharmacol Exp Ther 171 98 1970
49 Cohen M V, and Kirk E S Differential response of large and small coronary arteries to nitroglycerin and angiotensin Autoregulation and tachyphylaxis Circulation Res 33 445 1973
50 Zelis R Mason D T, Spann J F, and Amsterdam E A The mechanism of action of nitroglycerin in the relief of angina pectoris Reduction of myocardial oxygen requirements by vasodilation and its attenuation by the chronic administration of isosorbide dinitrate Ann Intern Med 72 779 1970
51 Zelis R, and Mason D T Isosorbide dinitrate Effect on the vasodilator response to nitroglycerin J A M A 234 166 1975
52 Parmley W Personal communication 1979
53 Chatterjee K Personal communication 1979
54 Cohn J N Personal communication 1979
55 Muller J E and Gunther S J Nifedipine therapy for Prinzmetal's angina Circulation 57 137 1978
56 Aronow W S Medical treatment of angina pectoris II Design of an antianginal drug study Am Heart J 84 132, 1972
57 Stipe A A and Fink G B Prophylactic therapy of angina pectoris with organic nitrates Relationship of drug efficacy and clinical experimental design J Clin Pharmacol 13 244 1973
58 Winsor W and Berger H J Oral nitroglycerin as a prophylactic antianginal drug Clinical physiologic and statistical evidence of efficacy based on a three phase experimental design Am Heart J 90 611 1975
59 Cole S L and Kaye H Antianginal effects of oral controlled release nitroglycerin in patients with coronary artery disease Double blind randomized multiple cross over study Clin Res 23 177 1975
60 Davidov M F and Mroczek W J The effect of sustained release nitroglycerine capsules on anginal frequency and exercise capacity Angiology 28 181 1977
61 Reichek N Goldstein R E Redwood D R and Epstein S E Sustained effects of nitroglycerin ointment in patients with angina pectoris Circulation 50 348 1974
62 Goldstein R E Rosing D R Redwood D Beiser G D and Epstein S E Clinical and circulatory effects of isosorbide dinitrate Comparison with nitroglycerin Circulation 43 629 1971
63 Lee G Mason D T Amsterdam E A Miller R R and DeMaria A N Antianginal efficacy of oral therapy with isosorbide dinitrate capsules Chest 73 327 1978
64 Cohn J N Mathew K J Franciosa J A and Snow J A Chronic vasodilator therapy in the management of cardiogenic shock and intractable left ventricular failure Ann Intern Med 81 177 1974
65 Gray R Chatterjee K Vyden J Ganz W Forrester J S and Swan H J C Hemodynamic and metabolic effects of isosorbide dinitrate in chronic congestive heart failure Am Heart J 90 346 1975

66. Kovick R B., Tillisch J H., Berens S C Bramowitz A. D and Shine K I Vasodilator therapy for chronic left ventricular failure Circulation 53 322, 1976
67 Massie B Chatterjee K Werner J Greenberg B Hart R and Parmley W W Hemodynamic advantage of combined administration of hydralazine orally and nitrates nonparenterally in the vasodilator therapy of chronic heart failure Am J Cardiol 40 794 1977
68 Chandraratna P A N Langevin E., O Dell R Rubinstein C and San Pedro S Use of nitroglycerin ointment in congestive heart failure Cardiology 63 337 1978
69 Mehta J., Pepine C J and Conti C R Non parenteral combined afterload and preload reduction therapy in congestive heart failure Clin Cardiol 1 68 1978
70 Battock D and Chidsey C A Isosorbide dinitrate in angina Circulation 44 1147 1971
71 Hirschleifer I Nitroglycerin Clinical pharmacological effects of form and route of administration Curr Ther Res 15 616 1973
72 Danahy D T., and Aronow W S Hemodynamics and antianginal effects of high dose oral isosorbide dinitrate after chronic use Circulation 56 205 1977
73 Lee G Mason D T and DeMaria A N Effects of long term oral administration of isosorbide dinitrate on the antianginal response to nitroglycerin Absence of nitrate cross tolerance and self tolerance shown by exercise testing Am J Cardiol 41 82 1978
74 Franciosa J A and Cohn J N Sustained hemodynamic effects of nitrates without tolerance in heart failure Circulation 58(Suppl 2) 28 1978

Clinical pharmacology of the new beta-adrenergic blocking drugs Part 9 Nadolol A new long-acting beta-adrenoceptor blocking drug

William Frishman M D
Bronx N Y

The value of beta adrenergic blockade in arterial hypertension angina pectoris and arrhythmias has been well established during the last decade[1] An increasing number of beta blockers with varying pharmacodynamic and pharmacokinetic properties have recently been introduced into clinical practice

Nadolol (SQ 11 275) is a new non cardioselective beta adrenergic blocking agent which was developed in the United States It has a unique pharmacological property in that it has the longest plasma half life of any known beta blocking drug and can be administered once daily[2]

The clinical experience with nadolol is now being gathered world wide in angina pectoris arrhythmias and hypertension The first clinical ... in the United States have been completed ... ig nadolol for the treatment of hypertension and angina pectoris In this article the clinical pharmacology efficacy and toxicity of this promising new agent will be described and its potential therapeutic applications will be discussed

Pharmacodynamic and pharmacokinetic properties (Table I)

Nadolol 2 3 cis 1 2 3 4 tetrahydro 5 [(2 hydroxy 3 tert butylamine)] propoxy 2 3 naphthalenediol (Fig 1) is a non selective β adrenoceptor

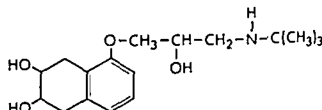


Fig 1 Structural formula of the β adrenoceptor blocking drug nadolol

blocking drug which lacks both membrane stabilizing and intrinsic sympathomimetic activity (partial agonist activity)[3] It has a level of potency which is two to four times that of propranolol[3] Compared to propranolol nadolol (probably related to its lack of membrane stabilizing effect) has been found to be approximately 50 to 500 times less depressant (contractility) to the isolated guinea pig atrium[5]

Nadolol is absorbed rapidly from the gastrointestinal tract achieving its peak effect in 3 to 4 hours[6] Only 30% of the oral dose is absorbed The drug is not metabolized in the body and is excreted unchanged in the urine (70% of absorbed dose) and via the bile in the feces (20% of absorbed dose)[4,6] Nadolol is 30% bound to plasma proteins[7] The drug has a plasma half life of 17 to 23 hours the longest of any known beta blocker[6,7] The plasma half life is even longer where there is renal dysfunction with elimination proportional to creatine clearance The drug can be removed with hemodialysis

Physiological and metabolic effects (Table II)

The hemodynamic effects of nadolol are attributable to β adrenoceptor blockade In human

From th Di ision of C rd logy D p rtm t f Medi in Albert Einstein Colleg of Med i B o x N Y

Supported in p rt by United St tes P bli H lth Serv T ini g Gra t HL 070 1-09

Recei ed for publication Oct 10 19 9

Reprint requests William Frishm n M D D o f C rd l gy Albert Einst in College of Med n 1300 M s P k A Br n N Y 10461

D Frishman is a Te ching Scholar f th An n H art Associa ti n

0002-8 03/80/010124 + 05$00 50/0 © 1980 The C V Mosby Co

Table I Pharmacological properties A comparison between propranolol and nadolol

Pharmacologic property	*Propranolol*	*Nadolol*
Beta blockade potency ratio (propranolol = 1)	1	2-4
Cardioselectivity	0	0
Partial agonist activity	0	0
Membrane stabilizing activity	+	0
Extent of absorption (% of oral dose)	>90	≃30
First pass hepatic metabolism	+	0
Protein binding (%)	≃90	≃30
Elimination half life (hours)	3.5-6	17 24
Urinary and fecal recovery of unchanged drug (% of oral dose)	<1	>90
Active metabolites	+	0

Table II Hemodynamic and electrophysiologic effects of propranolol and nadolol*

Hemodynamic parameter	*Propranolol*	*Nadolol*
Resting heart rate	↓	↓
Exercise induced increment in heart rate	↓	↓
Peripheral resistance	↔	↔
Effect on blood pressure (rest)	↓	↓
Exercise induced increment in blood pressure	↓	↓
Cardiac contractility	↓	↓ ↔
Cardiac output	↓	↓
Effect on elevated plasma renin	↓	↓
Effect on atrioventricular conduction	↓	↓

*In dosages giving similar degree of beta blockade

studies nadolol like propranolol reduces cardiac contractility and work In a hemodynamic study of 14 patients with coronary artery disease both nadolol and propranolol (in similar beta blocking doses) reduced heart rate cardiac index stroke work ejection fraction dp/dt and Vmax peripheral resistance rose slightly [9] The cardiocirculatory effects of nadolol and propranolol were similar In another study employing radionucleotide techniques to evaluate left ventricular function in patients with coronary artery disease both nadolol and propranolol (in equivalent beta blocking concentrations) reduced the ejection fraction [6]

The findings of the above studies differ from the results of animal experiments where nadolol was found to have less myocardial depressing effect than propranolol These experiments were done in the isolated guinea pig atria and the membrane stabilizing action of propranolol may have been important with the concentrations of drug used [3]

In several experimental studies nadolol has been demonstrated to be effective against cardiac arrhythmias [4] As seen with other beta blocking agents this antiarrhythmic activity appears to be related to β adrenergic receptor blockade an action that would antagonize the capacity of catecholamines to induce arrhythmias by alteration of cardiac automaticity and conductivity [4,1,1]

Nadolol was effective in antagonizing ectopic activity occurring during vagal induced depression of primary pacemaker activity presumably by inhibiting the actions of catecholamines on the automaticity of the ectopic pacemaker Both nadolol and propranolol antagonized isoproterenol induced tachycardia and oubain induced arrhythmias in cats The two agents also antagonized coronary artery ligation induced ventricular fibrillation In contrast to propranolol nadolol was considerably weaker in suppressing existing digoxin induced arrhythmias and lacked membrane stabilizing activity Both nadolol and propranolol depress atrioventricular conduction The duration of beta blocker effect was five times greater with nadolol than with propranolol [4]

Nadolol has been shown to have similar effects on glucose and lipid metabolism as propranolol[33] With regards to other physiologic parameters (effects on the bronchial tree platelet function hemoglobin oxygen dissociation) there is insufficient data

Nadolol has been shown both in animal experiments and in human trials to lower pre treatment plasma renin activity as much as 50%[7 34] This decrease in plasma renin activity is in the same range as earlier reported for hypertensive patients treated with propranolol In preliminary studies (animal and human) nadolol has been shown to increase renal blood flow This finding contrasts with the observations made with all other beta blocking drugs where renal blood flow has been shown to decrease due to decreased cardiac output The mechanism for this paradoxical renal blood flow effect with nadolol has not been elucidated

Therapeutic applications and clinical experience

The hemodynamic and pharmacokinetic profile of action of nadolol suggested its application in cardiovascular disorders such as hypertension[1 3] ischemic heart disease and cardiac arrhythmias

Hypertension It is well recognized that beta adrenergic blocking agents are effective in controlling the blood pressure of many patients with hypertension As mentioned previously there is no consensus of opinion as to the mechanism or mechanisms by which these drugs lower blood pressure Moreover there appears to be no difference in therapeutic efficacy between the different beta blockers (with a similar degree of β blockade) in hypertension[1]

Nadolol has proven to be a safe and effective antihypertensive agent when compared with placebo A preliminary single blind study was carried out with nadolol in ?0 untreated patients with essential hypertension After a 2 week period on placebo patients were treated for 14 weeks with daily doses of 40 mg nadolol (20 mg twice daily) Dosage was increased every second week up to a maximum of 560 mg daily until the patient was stabilized at an effective normotensive dose level Compared to placebo there was a significant reduction in both systolic and diastolic blood pressure (approximately 24/21 mm Hg) at an average daily dose of 110 mg nadolol Pretreatment plasma renin activity value decreased by 50% as a result of 14 weeks treatment with nadolol This decrease in plasma renin activity is in the same range as earlier reported for hypertensive patients treated with propranolol Apart from a tendency to bradycardia no other side effects were reported

The long half life of nadolol in serum suggested the possibility of administering the drug only once a day Many trials are currently in progress comparing the efficacy of oral nadolol administered once daily with propranolol administered four times daily

A drug which can be taken once daily could enhance patient compliance in the treatment of hypertension Studies have shown that patient compliance in hypertension varies with the complexity of the dosing regimens[1 4] In one large study of a hypertensive population only 5% of patients given a diuretic *failed to take the* prescribed dose (once a day regimen) presumably due to the simple therapeutic regimen whereas the proportion not taking alpha methyldopa propranolol and reserpine (multiple dose regimen) approached 30%[1] This lack of patient compliance was unrelated to side effects

Would a beta blocking drug with a 24 hour half life therefore be an advantage in the therapy *of hypertension? Propranolol* and oxprenolol have comparatively short half lives and if this alone determined the frequency of drug dosage these agents would need to be given at least four times daily However the physiological effect of beta blockade upon blood pressure substantially outlasts the survival of unchanged drug in the plasma twice or even once daily dosage seems adequate[2 31] Therefore preparations with a long pharmacokinetic half life such as nadolol atenolol or slow release preparations of drugs such as oxprenolol may confer no great advantage

Angina pectoris Multiple studies have demonstrated *the effectiveness of beta* adrenoceptor blocking agents for the treatment of patients with angina pectoris As described previously these drugs reduce the determinants of myocardial oxygen consumption enabling a patient to do *more work*[2 17]

A randomized double blind study was carried out in 24 patients with stable angina pectoris to compare the efficacy of nadolol and propranolol[**] After a period on placebo 14 patients received nadolol once daily and 10 patients received

propranolol four times daily over a 10 week dose finding period followed by a maintenance period of 4 weeks The optimal daily dosage for nadolol was 100 mg and 112 mg for propranolol The parameters used for evaluation of therapeutic effectiveness included the number of anginal attacks number of nitroglycerin tablets needed time before onset of chest pain during an exercise test exercise time and over all clinical impression Nadolol and propranolol were equally effective in reducing anginal attacks and nitroglycerin consumption Similarly exercise tolerance was improved with both drugs

It was concluded from this study that nadolol once a day is as effective as propranolol four times daily in treating patients with angina pectoris

A beta blocker that can be given just as a single daily dose for angina pectoris might be a factor of major importance in ensuring patient compliance What is not known at this time however is whether other beta blockers with shorter half lives can also be given once or twice daily for angina pectoris

A larger multicenter trial in this country comparing nadolol once daily with placebo and propranolol taken four times daily has been completed The published results are being awaited with great interest

Arrhythmias Nadolol has been shown to be an effective treatment for cardiac arrhythmias As demonstrated with all beta adrenoceptor blocking drugs its antiarrhythmic properties stem from the ability to antagonize the effects of catecholamines on cardiac automaticity and conductivity

Nadolol was initially developed as an antiarrhythmia agent in 1973 Although the electrophysiological properties of the drug are well known there is no large clinical data base to date

In one study 29 patients with frequent ventricular and supraventricular ectopic beats and other supraventricular arrhythmias received sequential doses of placebo and nadolol Dose titration and nadolol maintenance were accomplished during a four week period on doses up to 100 mg/day preceded and followed by placebo periods extending to two weeks Ectopic activity was monitored by Holter 24 hour dynamic electrocardiography A reduction or remission of arrhythmia was observed in approximately two thirds of patients Arrhythmias that responded favorably involved ventricular bigeminy paroxysmal atrial tachycardia and sinus tachycardia Patients with atrial flutter or fibrillation did not convert to normal sinus rhythm however all patients had a favorable reduction in ventricular response Maintenance doses most frequently used were 60 to 160 mg/day in single or divided doses Reductions in resting heart rate and arterial pressure consistent with beta adrenoceptor blockade were observed It was concluded from this trial that nadolol might be of value in the treatment of cardiac dysrhythmias

A beta adrenoceptor blocking agent with a long half life that can be administered to patients once daily for management of cardiac arrhythmias might prove extremely useful in clinical practice Trials with nadolol in one daily dose compared with other beta blockers and other antiarrhythmic agents are still necessary for evaluating the agent in the acute and chronic treatment of patients with cardiac dysrhythmias

Side effects and toxicity

In the limited clinical experience to date nadolol has side effects similar to other beta adrenoceptor blocking drugs (i e propranolol) No unusual toxic effects have been demonstrated and carcinogenicity study requirements have been met

One potential problem with chronic nadolol administration might be the toxic accumulation of drug in the plasma of patients with impaired renal function With its long half life lack of hepatic metabolism and renal elimination property nadolol dosage must be varied according to the serum creatinine[6] In situations where toxic levels of the drug might accumulate the drug is dialyzable

Therapeutic implications and conclusions

Nadolol is an effective beta adrenoceptor blocking agent with the longest half life among the compounds of this class This property would enable the drug to be administered once daily and clinical studies have substantiated the effectiveness of this regimen With the common problem of patient compliance daily in hypertension arrhythmia and angina pectoris where multidose regimens are used an agent which can be taken once daily would provide a major advantage

On the other hand recent studies have suggested that the beta adrenoceptor bl

drugs with short half lives have longer pharmaco dynamic actions which might obviate the need for their frequent dosing

Until this crucial pharmacological issue is resolved nadolol appears to be an important pharmacological advance

REFERENCES

1 Frishman W., and Silverman R Clinical pharmacology of the new beta adrenergic blocking drugs Part 2 Physiologic and metabolic effects AM HEART J 97 797 1979
2 Frishman W Clinical pharmacology of the new beta adrenergic blocking drugs Part 1 Pharmacodynamic and pharmacokinetic properties AM HEART J 97 663 1979
3 Lee R J Evans D B Baky S H and Laffan R J Pharmacology of nadolol (SQ 11 725) a beta adrenergic antagonist lacking direct myocardial depression Eur J Pharmacol 33 371 1975
4 Evans D B Peschka M T Lee R J and Laffan R J Antiarrhythmic action of nadolol a beta adrenergic receptor blocking compound Eur J Pharmacol 35 17 1976
5 Lee R J, Evans D B Baky S H and Laffan R J The cardiovascular pharmacology of SQ 11 725 (SQ) a potent beta adrenergic antagonist lacking significant myocardial depressant activity (Abstract) Fed Proc 32 780 1973
6 Dreyfuss J Brannick L J Vukovich R A Shaw J M and Willard D A Metabolic studies in patients with nadolol oral and intravenous administration J Clin Pharmacol 17 300 1977
7 Vukovich R A Dreyfuss J Brannick L J Herrera J and Willard D A Pharmacologic and metabolic studies with a new beta adrenergic blocking agent nadolol Clin Res 24 592 1976
8 Wong K K Dreyfuss J Shaw J M Ross J J, Jr., and Schreiber F C A beta blocking agent (SQ 11 725) that is not metabolized extensively by dogs and monkeys (Abstract) Pharmacologist 15 245 1973
9 Lee G DeMaria A N Miller R R Joye J A Baker L Jameson L Low R and Mason D T Comparative effects of nadolol and propranolol on cardiac and peripheral circulatory function in patients with coronary artery disease Clin Res 26(2) 100A 1978
10 LeWinter M M Curtis G Shabetai R Verba J Bloomquist J and Engler R Comparison of the effects of a new beta adrenergic blocking agent (nadolol) and propranolol on left ventricular performance in patients with prior myocardial infarction Clin Res 26(2) 101A 1978
11 Peschka M Evans D B and Laffan R J Antiarrhythmic activity of SQ 11 725 (SQ) a potent nondepressant beta adrenergic blocking agent (Abstract) Fed Proc 32 780 1973
12 Gibson J K Gelband H, and Bassett A L Possible basis of antiarrhythmic action of a new beta adrenergic blocking compound (Abstract) Am J Cardiol 37 138 1976
13 Gibson J K, Gelband H and Bassett A L Effects of SQ 11 725 on the electrophysiology of isolated mitral cardiac tissue (Abstract) Pharmacologist 16 201 1974
14 Vukovich R A, Sasahara A Zambrano P Belko B S Godin P and Brannick L J Antiarrhythmic effects of a new beta adrenergic blocking agent nadolol, Clin Pharmacol Ther 19 118 1976
15 McKinstry D N Vukovich R A and Willard D A Effects of beta adrenergic blockade with nadolol and propranolol on glucose and lipid metabolism in man Clin Res 25(3) 548A 1977
16 Frithz G Dose ranging study of the new beta adrenergic antagonist nadolol in the treatment of essential hypertension Curr Med Res Opin 5 383 1978
17 Frishman W, and Silverman R Clinical pharmacology of the new beta adrenergic blocking drugs Part 3 Comparative clinical experience and new therapeutic applications AM HEART J 98 119 1979
18 Bulpitt C J, and Dollery C T Side effects of hypotensive agents evaluated by a self administered questionnaire Br Med J 3 485 1973
19 Caldwell J R Cobb S, Dowling M D and DeJongh, D The drop-out problem in antihypertensive treatment J Chronic Dis 22 579 1970
20 Berglund G, Anderson O, Hansson L, and Olander R Propranolol given twice daily in hypertension, Acta Med Scand 194 513 1973
21 Wilson M, Morgan G, and Morgan T The effect of blood pressure of β adrenoreceptor blocking drugs given once daily Clin Sci Mol Med 51 527s 1976
22 Furberg B Dahlqvist A, Raak A and Wrege U Comparison of the bew beta adrenoceptor antagonist nadolol and propranolol in the treatment of angina pectoris Curr Med Res Opin 5 388 1978
23 Status report on beta blockers, FDA Drug Bulletin 8 13 1978

The Canadian trial of aspirin and sulfinpyrazone in threatened stroke

There is good evidence that in a large percentage of patients with transient focal cerebral ischemic attacks (TIA s) platelet fibrin emboli are dislodged from an atherosclerotic ulcerative and stenotic lesion in a major cervical artery and then occlude one or more intracranial or retinal arteries. Data from a community study of TIA indicate that the peak period of stroke occurrence is within the first few months following the onset of TIA

Endarterectomy which is applicable primarily to patients with carotid TIA is aimed at eliminating the lesion which allows accumulation of platelet fibrin material Anticoagulant treatment should prevent formation of fibrin that maintains the stability of a beginning platelet thrombus Antiplatelet drugs may prevent platelet aggregation or more importantly should prevent adherence of platelets to an area of endothelial injury

The Canadian trial of antiplatelet drug in "threatened stroke is a well designed study and there are few important faults with the methodology described in the publication It is important to note that there were almost as many patients excluded from the study as were randomized and this raises questions about whether the group randomized was representative of TIA in general It is also relevant that 46% of the patients included had neurologic residua at the time of entry into the study strictly speaking these patients had small cerebral infarcts not TIA We simply do not have data on whether strokes of that type are comparable to TIA

The number of months between the first TIA and randomization was similar in each group studied and this is important because the greatest risk of stroke is soon after the onset of TIA There were 24% over age 70 among patients not treated with either drug in contrast to about 15% in the other three groups This may seem to be a bias against those untreated patients however the fact of occurrence of TIA in a patient greatly overrides the effect of age in regard to stroke probability so that weighting may not be important

One of the objectives of the Canadian trial of aspirin and sulfinpyrazone in patients with TIA was to determine in four groups of patients whether aspirin sulfinpyrazone or both would reduce the occurrence of first stroke or recurrent stroke when compared to an untreated group If one compares those four groups independently the study did not show a difference among the four groups Table V of the publication assuming that the patient months of observation were similar indicates that among the patients treated with aspirin alone there were 2? strokes and among those that received no treatment there were 20 strokes Among the men who received aspirin alone there were 14 strokes and there were 15 strokes among those men who received no treatment

The publication emphasizes the combination of stroke plus death as endpoints for combinations of the four groups of patients However there is an important problem with that approach Among patients with TIA only about 25% of deaths are due to stroke nearly 50% are due to heart disease and 25% to other causes most of which are non vascular The approach used by these investigators, in effect aims to assess stroke plus death due to heart disease or at least heavily weighted for heart disease There would be no argument if the analysis was concerned only with mortality but that would be a hopeless proposition for comparison nor would there be argument with the assessment of all strokes and all cardiac events without regard to death In the latter circumstance if the pathophysiology is different for the different types of endpoints, and that is a possibility a beneficial effect in regard to stroke could be masked

It is feasible to assess the effect on stroke occurrence exclusive of other considerations This may be done by constructing a table comparable to a mortality table or the complement of a life table and using actuarial analysis with stroke as the endpoint rather than death Each interval assessed determines the probability of stroke (with or without death) by the number of persons who have had a stroke in the interval divided by the number of persons under observation times 100

When a person is lost to follow up or is withdrawn for any reason that person is removed from the denominator of the fraction Those who die from a cause other than stroke are no longer at risk for stroke so are also removed from the denominator or from those under observation but are not counted as endpoints Of course this is not a real life situation and one cannot ignore the risk of death in a drug trial but that can be assessed separately This technique does allow a time-based judgement of the effect on stroke exclusive of other disorders affecting the study population This type of actuarial analysis has been used for other studies of the effect of treatment on stroke occurrence

Table IV in the Canadian study shows the results in the four groups of patients The expected number of events was determined by a proportional share of all events among the patients Assuming that the patient months of observation were similar in the aspirin groups and the non aspirin groups, one can calculate from the data that there was approximately a 26% reduction in stroke among those taking aspirin However that difference is not significant For males there was a 49% reduction which was significant however it is not appropriate to examine subgroups for significance when the over all comparison is not significant If one analyzes the many variables involved in the subgroups, it should result in 1 out of 20 being significant on the basis of chance alone The observed difference between men and women is intriguing and does deserve further study

The graph in Fig 1 from the publication shows the kind of cumulative probability of stroke analysis to which I previously referred but this also includes death The discordant group

000? 8/03/80/0101?9 + 0?$00 20/0 © 1980 The C V Mosby Co

is the one which included men who were on aspirin plus sulfinpyrazone so at least in males the two drugs may be more beneficial than either one alone

There are no data which allow satisfactory comparison of carotid endarterectomy anticoagulant therapy and antiplatelet therapy for treatment of TIA The probability of stroke for a normal population age 65 to 74 years is about 1% per year When TIAs have been present for more than several months the probability of stroke is about 6% per year without treatment The extracranial occlusive disease study indicated that the probability of stroke was about 3.5% per year following surgery but if the surgical morbidity was excluded it was less than 2% per year Among all of the anticoagulant studies of the treatment of TIA controlled and uncontrolled, the highest annual stroke rate noted is 3% per year and that figure came from a population study which began at the onset of TIA Taking the observations of the Canadian study literally the probability of stroke in men taking aspirin was in excess of 5 per year and in women was greater than 8% per year For men taking aspirin and sulfinpyrazone the stroke probability was greater than 2% per year

These probabilities of stroke cannot be directly compared as there is no way to assess whether the different groups studied were in any way comparable It is clear that patients with TIA have a greatly increased risk of stroke compared to a normal population but it is difficult to establish with certainty a difference in stroke probability based on the effects of various types of treatment that have been proposed

Our preference for treatment of TIA at present is surgical if an appropriate carotid lesion is present but that must presume a surgical experience with not much over 1% combined stroke morbidity and mortality If surgical treatment is not appropriate anticoagulant treatment is preferred at the onset of TIA for the first few months when there appears to be the greatest benefit with the least risk Since there may be a modest benefit from aspirin treatment we recommend treatment with aspirin after the cessation of anticoagulant therapy and then discontinuation of the aspirin at one year after the onset of TIA unless there is recurrence of symptoms.

Jack P Whisnant MD
Professor and Chairman
Department of Neurology
Mayo Clinic & Mayo Medical School
Rochester Minn 55901

REFERENCES

1 Whisnant J P, Matsumoto N and Elveback L R The effect of anticoagulant therapy on the prognosis of patients with transient cerebral ischemic attacks in a community Rochester Minnesota 1955 through 1969 Mayo Clin Proc 48 844 1973
2 A randomized trial of aspirin and sulfinpyrazone in threatened stroke—The Canadian cooperative study group N Engl J Med 299 53 1978
3 Cartlidge N E F, Whisnant J P and Elveback L R Carotid and vertebral basilar transient cerebral ischemic attacks A community study Rochester Minnesota Mayo Clin Proc 52 117 1977
4 Whisnant J P, Cartlidge N E F and Elveback L R Carotid and vertebral basilar transient ischemic attacks Effect of anticoagulants hypertension and cardiac disorders on survival and stroke occurrence—A population study Ann Neurol 3 107 1978
5 Fields W S, Maslenikov V, Meyer J S Hass W K Remington R D and Macdonald M Joint study of extracranial arterial occlusion V Progress report of prognosis following surgery or nonsurgical treatment for transient cerebral ischemic attacks and cervical carotid artery lesions J A M A 211 1993 1970
6 Sandok B A, Furlan A J Whisnant J P and Sundt T M Guidelines for the management of transient ischemic attacks Mayo Clin Proc 53 665 1978

Excessive proneness of Jews to ischemic heart and bowel diseases

Abu Zeid and co workers have recently reported on Ethnic differences in mortality from ischemic heart disease a study of migrant and native populations observations related to Manitoba for the period 1960 to 1971 It transpired that a much higher risk of mortality than the expected was found among Canadian born Jews The disparity was much more marked for males than for females The standardized mortality (I C D rubric 420) ratio for males was 166 3 This figure was by far the highest of the 2 ethnic male populations studied, and indicated a mortality rate from the disease among the highest yet reported This much higher than average mortality rate in Canadian born male Jews confirms earlier observations made in New York in 19 which revealed that manifest ischemic heart disease (IHD) in a Jewish male group was double that found in an Italian male group

In Johannesburg South Africa in 1960 the ratio of crude mortality rate from IHD (I C D rubric 420) for non-Jewish compared with Jewish males was 1 1 75 Later in 19 2 the corresponding ratio was 1 1 71 For the roughly 380 000 non Jews and 60 000 Jews (both sexes) in Johannesburg crude non standardized death rates from IHD were roughly 230 and 3 0 per 100 000 respectively IHD being responsible for approximately 22 and 37% respectively of all deaths of non-Jews and Jews As a comparison it is highly illuminating to note that in Tel Aviv Israel in 1974 IHD was reported as being responsible for 38% of all deaths

In Scotland a very high mortality rate from IHD is associated with a very high mortality rate from colon cancer It is therefore important to note that the crude colon cancer mortality rate for Johannesburg Jews (males and

0002 8703/80/010130 + 02$00 20/0 © 1980 The C V Mosby Co

females combined) for the period 1968 to 1972 was found to be (1) double that of non-Jewish Whites and (2) four times that for the population of Israel Differences in values between the sexes was slight The rate for total Johannesburg Jews was 25 per 100 000 the same as that for the population of Scotland for the same period—whose rate was the highest of values reported for national populations. Remarkably no such disparities prevailed for rectal cancer Furthermore a recent survey has indicated that the prevalence of ulcerative colitis (a risk factor for colon cancer) in Johannesburg Jews is more than double that prevailing for the non-Jewish White moiety A report from Baltimore indicated the corresponding differential to be even greater

Our preliminary dietary studies by one of us (C H) on groups of Jews in Tel Aviv and in Johannesburg have indicated no outstanding differences in average intakes of gross dietary components although in the Johannesburg group greater proportions of the fat and protein moieties are derived from animal sources However undoubtedly there were greater disparities in dietary patterns 10 to 20 years ago

Finally there is evidence that for Jews in the USA expectation of life at 65 years is decreasing in contrast to that of most other populations

We certainly would not wish to unduly press the accuracy of our data nevertheless the very excessive proneness of Johannesburg Jews to the diseases mentioned is judged to be beyond dispute

We very much doubt whether the phenomena are explicable wholly on the basis of differences in environmental factors particularly diet We consider that not only individuals but ethnic groups such as Jews may be *programmed* with the weaknesses described which becomes more prominent with rise in sophistication of diet and manner of life It may be recalled that Burch entertained the possibility that Negroes in the USA may be programmed for an expectation of life shorter than that of the White inhabitants

It would seem very important that in cities or regions where major differentials in morbidity and mortality from particular diseases prevail between Jewish and non Jewish Whites there should be intensive characterizations of diet and biological variables It should then be possible to learn *inter alia* to what extent similarities in these variables evoke or are consistent with differences in pathology

A R P Walker D.Sc
South African Institute for Medical Research
Johannesburg
I Segal M B B Ch., M R C P
Baragwanath Hospital
Johannesburg South Africa
T Gilat M.D
C Horowit Ph.D
Ichilov Hospital
Tel Aviv Israel

REFERENCES

1 Abu Zeid H A H Maini K K and Choi N W Ethnic differences in mortality from ischemic heart disease A study of migrant and native populations J Chronic Dis 31 137 1978
2 Annual Global Data on Mortality 1970-1972 Ischemic Heart Disease (B.28) World Health Statistical Report 27 82 1974
3 Epstein F H Boas E P and Simpson R The epidemiology of atherosclerosis among a random sample of clothing workers of different origin in New York City J Chronic Dis 5 300 1957
4 Walker A. R P Extremes of coronary heart disease mortality in ethnic groups in Johannesburg South Africa AM HEART J 66 293 1963
5 Statistical Year Book No 15 Tel Aviv Yafo Municipality Department of Research and Statistics 1975 p 323
6 Logan W P D Cancer of oesophagus stomach intestine and rectum International mortality patterns and trends World Health Statistical Report 28 473 1975
7 Israel Cancer Registry Cancer in Israel—Facts and Figures for 1967 1971 Jerusalem Ministry of Health September 1977 p 32-35
8 Mendeloff A I Monk M., Siegel, C I and Lilienfeld A Illness experience and life stresses in patients with ulcerative colitis N Engl J Med 282 14 1970
9 Fauman S J and Mayer A J Jewish mortality in the U.S., Hum Biol. 41 416 1969
10 Burch G E People are not living longer any more AM HEART J 83 285 1972

The clinical value of cardiac fluoroscopy

In 1962 Erich Zdansky wrote in his famous classical work Roentgendiagnostik des Herzens und der grossen Gefas e" (Roentgen diagnosis of the heart and great vessels) Even today thorough fluoroscopy is an integral part of the roentgenologic examination of the heart and great vessels For a long time fluoroscopy was a powerful tool in the hand of the cardiovascular radiologists and cardiologists for the evaluation of the cardiac chambers and great vessels

In the last 20 years reliable electrocardiographic criteria for hypertrophy and dilatation of the heart chambers were developed more recently ultrasonography was introduced as a valuable diagnostic tool in the diagnosis of various abnormal heart conditions cinefluorography has becom another new modality in the diagnosis of heart diseases Considering these new developments it appears appropriate to review the role of conventional fluoroscopy in differential diagnosis of the heart diseases

In our experience the standard four views of the chest with barium swallow obtained preferably with high kV technique have replaced fluoroscopy in the evaluation of cardiac chamber enlargement On good films the heart is seen without magnification and its configuration can be [illegible] ure Correlation between pulmonary vasc [illegible] ize and shape can be readily made The [illegible] ions

of the pulmonary artery by fluoroscopy is highly subjective and the so-called typical hilar dance is rarely observed

The patient's radiation exposure is 50 to 100 times greater for one minute of fluoroscopy than for a single PA chest radiogram. Thus fluoroscopy represents a significantly higher radiation hazard which is particularly important in the pediatric age group. However, there remain some indications for cardiac fluoroscopy which should no longer be performed on a routine basis.

If valvar calcifications are to be demonstrated, fluoroscopy or preferably cinefluorography is the procedure of choice. But nowadays the same diagnosis can be made without ionizing radiation, namely by ultrasonography. However, small coronary artery calcifications are detectable only during fluoroscopy. In both groups of patients fluoroscopy does not have to be performed as a separate procedure. Most of these patients came to cardiac catheterization or coronary arteriography and thus calcifications can be seen on the angiographic studies.

The function of the artificial prosthetic valves can be well studied by fluoroscopy or preferably by cineradiography. For the visualization of the movement of artificial discs and valve leaflets a C arm is very helpful because a true end on view has to be obtained for the detection of these extremely thin structures. Admittedly, similar information can be obtained nowadays by two dimensional ultrasonography.

Fluoroscopic evaluation of ventricular aneurysms is not indicated. Paradoxical pulsations are virtually never seen. Akinetic areas are usually not appreciated. Aneurysms or contraction abnormalities can only be excluded with certainty by cine left ventriculography. Transmitted pulsations cannot be distinguished from true pulsation. This is the reason why fluoroscopy does not allow differentiation of mediastinal masses from aortic aneurysms.

The diagnosis of pericardial effusion used to be a good indication for fluoroscopy. In recent years, however, it was replaced by ultrasonography which is much more sensitive.

In summary, few indications remain. Cardiac fluoroscopy has been largely replaced by better and more diagnostic, less hazardous tests. In carefully selected patients it remains a useful diagnostic tool, but its indiscriminate and routine use is no longer justified.

Agustin Formanek, M.D.
Associate Professor of Radiology
Variety Club Heart Hospital
Dept. of Radiology
University of Minnesota Hospitals
Minneapolis, Minn. 55455

REFERENCES

1. Zdansky, Erich: Roentgendiagnostik des Herzens und der Grossen Gefasse. 3rd edition. Vienna, 1962, Springer-Verlag.
2. Johns, H. E., and Cunningham, J. R.: The Physics of Radiology. 3rd edition. Springfield, Illinois, 1974, Charles C Thomas, Publisher.

Of T waves and chronic congestive heart failure

Chronic congestive heart failure (CHF) is always associated with T wave abnormalities in the electrocardiogram. Abnormal T waves are a reliable diagnostic confirmation of chronic CHF. Beware of a diagnosis of chronic CHF in the absence of abnormal T waves in the ECG.

George E. Burch, M.D.
Tulane University School of Medicine
and Charity Hospital of Louisiana
New Orleans, La.

0002-8703/80/010132 + 01$00.10/0

Surgical closure of coronary artery fistula emptying into left ventricle

To the Editor

We read with interest Drs Arani, Greene and Klocke's report on coronary artery fistulas emptying into left heart chambers. We recently reported a case in which the fistula was surgically closed and presented a movie of same at the American Heart Association meeting in Anaheim California on November 17 1975 and at the American College of Chest Physicians meeting in Washington D C on November 1 1978 Our patient's fistula involved the main left anterior descending coronary artery and not a diagonal or contributing branch We congratulate the authors on their report but must point out that a more careful perusal of the recent surgical literature would have discovered our recent contribution to the understanding of this interesting anomaly

Allen I Midell M.D
Senior Attending Surgeon
Gustavo A Bermudez M.D
Chief of Cardiology
Department of Surgery
University of Chicago
950 East Fifty ninth St
Chicago Ill 60637

REFERENCES

1 Arani D T Greene D G and Klocke F J Coronary artery fistulas emptying into left heart chambers Am Heart J 96 438 1978
2 Midell A I Bermudez, G A. and Replogle R Surgical closure of left coronary artery-left ventricular fistula J Thorac Cardiovasc Surg 74 199 1977

Reply

To the Editor

Although Dr Midell's and Dr Bermudez's abstract regarding a case of coronary fistula emptying into the left ventricle was presented earlier their paper was published in August 1977 while our paper on coronary artery fistula emptying into the left heart chamber was submitted for publication in September 1977 We congratulate the authors for their successful closure of the left anterior descending-left ventricular fistula but would like to point out that in our case the fistula consists of a diagonal branch emptying into the left ventricle with a small shunt and in our judgment the risk of surgery outweighs the benefits

Djavad T Arani M.D
David G Greene M.D
Francis J Klocke M.D
State University of New York
at Buffalo School of Medicine
100 High St
Buffalo N Y 14203

Single daily dosing of propranolol in hypertension

To the Editor

In the treatment of hypertension perhaps the most difficult problem is patient medication compliance Since one reason for poor compliance is complex medication scheduling simplification of the therapeutic regimen should help improve compliance Although propranolol was originally recommended to be given in four doses daily twice daily dosing in the treatment of hypertension is now approved in the United States Single daily dosing of propranolol has been studied and appears safe and effective To our knowledge however there are no published American trials of single daily dosing of propranolol in hypertension. The current experimental investigation was conducted in an effort to provide further information on the feasibility of administering propranolol in a single daily dose

Seven patients (one female six males) with confirmed essential hypertension whose average diastolic blood pressure taken on three consecutive visits was > 90 mm. Hg and who were subsequently controlled with propranolol, were included in the study The disappearance of sound (the fifth Korotkoff phase) was used as an indication of diastolic blood pressure Average age was 50 years (range 25 to 61 years) and average daily dose of propranolol was 183 mg (range 40 to 320 mg.) All patients were concurrently on a diuretic (six patients on hydrochlorothiazide one patient on furosemide) With the exception of one patient who was also treated with prazosin 2 mg /day no other antihypertensives were given. No drugs or dosages were changed during the study and no patient who had a contraindication or relative contraindication to the use of propranolol was included in the study

After the nature and purpose of the study were explained and informed consent was obtained the patients were stabilized on twice daily doses of propranolol and were instructed to take their dose at 9 A.M. and 9 P.M. daily omitting their A.M. dose on study days Every two weeks for eight weeks blood pressure in the sitting standing and supine positions along with heart rate were recorded at 9 A.M., 12 hours after the last dose of propranolol Three minutes was allowed between each postural change At the end of eight weeks the patients total daily dose of propranolol was given as one dose After blood pressure and heart rate were recorded the propranolol was administered by the investigator at 9 A.M. with measurements recorded again two hours later (to reflect the approximate peak plasma concentration) Patients were then seen every two weeks for eight weeks with recordings taken 24 hours after the last dose (9 A.M.) and two hours later At each clinic visit the patients were questioned about possible adverse effects Mean blood pressures on twice daily and once daily therapy were compared using the Student's t test for dependent observations.

Mean systolic and diastolic blood pressures and heart rates are given for each regimen (Table I) Statistical comparison showed that blood pressure changes between twice daily

Table I Antihypertensive effects of single daily dosing vs twice daily dosing of propranolol

	Mean BPS (mm Hg) ± SEM				
	Twice daily 9 A.M.	*Difference twice daily to once daily (9 A.M.)*	*Once daily*		*Difference once daily 9 A.M.–11 A.M.*
			9 A.M.	*11 A.M.*	
Sitting—systolic	130 ± 2.3	p < 0.025	137 ± 3.4	129 ± 4.2	p < 0.05
diastolic	86 ± 1.8	NS	87 ± 2.3	84 ± 3.3	NS
Standing—systolic	131 ± 2.4	NS	131 ± 2.0	126 ± 2.5	p < 0.05
diastolic	88 ± 1.5	NS	89 ± 1.9	84 ± 2.1	p < 0.05
Supine—systolic	135 ± 3.2	NS	137 ± 3.3	130 ± 3.4	p < 0.05
diastolic	87 ± 0.9	NS	87 ± 2.0	84 ± 1.4	NS
Heart rate	70 ± 3	NS	73 ± 3	67 ± 2.4	p < 0.05

dosing at 9 A.M. and once daily dosing at 9 A.M. were not significant with the exception of the sitting systolic pressure which was significant ($p < 0.025$). This was due primarily to one patient whose mean systolic pressure increased from 132 to 148 mm Hg. While the mean heart rate increased on the once daily regimen, the difference was not significant. As expected, all blood pressures and heart rates decreased 2 hours after the once daily dose was given (Table I). While the decrease was statistically significant in most cases, no patient had to withdraw from the study due to bradycardia (HR < 50 beats/minute) or a hypotensive episode (decrease in diastolic blood pressure > 20 mm Hg) and no reduction in dose was necessary. Every patient was specifically questioned at each visit for known adverse effects to propranolol. Subjectively, there were no more adverse effects associated with once daily dosing than with twice daily dosing.

The results of this preliminary study indicate that single daily dosing of propranolol in hypertension is efficacious. In addition, this method of dosing appears to be safe. Results of other similar studies of propranolol are consistent with the findings of this investigation. Although more study with larger patient populations is certainly recommended in the United States before widespread use of this dosing regimen, some countries have already officially approved beta blockers for administration in single daily doses for the treatment of hypertension.

The explanation that probably contributes most to the prolonged antihypertensive action of propranolol has been described by Nies and Shand. As the single oral dose is increased above about 30 mg, the hepatic extraction process becomes saturated and remains saturated throughout the usual six hour dosing interval so that drug concentrations in the blood accumulate during chronic oral administration.

With recent research in the area of simplified regimens for beta blockers and other antihypertensive agents such as methyldopa and hydralazine, the prospect for exclusive twice a day and single daily dosing of all antihypertensive agents appears quite good.

James H. Patterson, Pharm.D.
Timothy H. Self, Pharm.D.
Wall[illegible] W[illegible]ke, Pharm.D.
Phillip E. Johnston, Pharm.D.
Stephen T. Miller, M.D.
William J. Bicker[illegible], M.D.
Depts. of Pharmacy Practice and Medicine
University of Tennessee Center for the Health Sciences
874 Union Ave.
Memphis, Tenn. 3816[illegible]

REFERENCES

1. Davidoff H F: Compliance with antihypertensive therapy: the last link in the chain. Conn Med 40:378, 1976.
2. Wilson M, Morgan G, and Morgan T: The effect on blood pressure of beta adrenoreceptor blocking drugs given once daily. Clin Sci Mol Med 51:527, 1976.
3. Gordon R D: Initial treatment of the young hypertensive: Thiazide diuretic or beta adrenoreceptor blocking agent in a single daily dose? Clin Sci Mol Med 51:631, 1976.
4. Wilson M, Morgan G, and Morgan T: The effect on blood pressure of beta adrenoreceptor blocking drugs administered once daily and their duration of action when therapy is ceased. Br J Clin Pharmacol 3:85, 1976.
5. Westerland A, and Hansson L: Once daily treatment of hypertension. Br Med J 2:877, 1976.
6. Frithz G: Initiation of once-daily pindolol treatment. Br Med J 1:300, 1978.
7. Nies A S, and Shand D G: Clinical pharmacology of propranolol. Circulation 52:6, 1975.
8. Wright J M, McLeod P J, and McCullough W: Antihypertensive efficacy of a single bedtime dose of methyldopa. Clin Pharmacol Ther 20:733, 1976.
9. O'Malley K, Segal J L, Israili Z H, et al: Duration of hydralazine action in hypertension. Clin Pharmacol Ther 18:581, 1975.

Regression equations and normal values for children

To the Editor:

The report of Lewis and associates on left ventricular function in β thalassemia is another example of the usefulness of the combined noninvasive techniques of systolic time intervals and echocardiography in investigating the effects of various disease states on left ventricular performance. In reporting their results, however, the authors presented the

deviations from normal of the various measurements without regard to the fact that normal values for children differ considerably from adults in many of these parameters

It has been known for some time that the relationship between systolic time intervals and heart rate in children is not identical to that in adults It is not therefore valid to apply the regression equations of Weissler to children as the authors did We have recently published regression equations which can be used as normal standards for children and which show that for a given heart rate the normal value for QS LVET and PEP can be quite different in children than in adults Even the ratio of PEP/LVET which is essentially independent of heart rate has a different normal value in children (0.30 ± 0 04) than in adults (0 35 ± 0 04) Similarly the normal values for adults for the chamber dimensions measured echocardiographically are not valid for children The normal chamber dimensions *per square meter of body surface area* are larger for children who have smaller body surface areas, than for adults Thus for example the upper limit of normal for left ventricular diastolic diameter for patient No 19 who had a body surface area of 0 70 M is 4 6 cm/M as opposed to 3.2 cm/M for adults

Approximately half of the 23 patients studied by the authors were children and in their Group 3 the majority were children It is not valid therefore to express the measurements in the entire series in terms of deviations from the normal values of adults For the same reason comparison of the three groups in respect to the mean values of the measurements as is shown by the authors in Figs 2, 3, and 5 and in Table III is not valid In order to compare the measurements in the three groups in such a mixed series, the percentage of deviation from normal should be calculated for each measurement based on the expected normal values for each individual It would be worthwhile for the authors to recalculate their data in this fashion in order to determine if there is really a significant difference as they reported between the groups in respect to some of the echocardiographic parameters More important it should be determined if there is not after all some degree of diminished left ventricular performance by systolic time intervals in Group 3

Kenneth L. Wanderman M.D
Director Noninvasive Laboratory
Cardiology Service
Soroka Medical Center and Faculty of Health Sciences
Ben Gurion University of the Negev
Beer Sheva Israel

REFERENCES

1 Lewis, B S., Rachmilewitz, E A., Amitai N., Halon D A., and Gotsman M S Left ventricular function in β thalassemia and the effect of multiple transfusions AM HEART J 96 636, 1978.

2 Cantor A Wanderman K L., Karolevitch T., Ovsyshcher I and Gueron M Systolic time intervals in children Normal standards for clinical use Circulation 58 1123 1978

3 Goldberg S J., Allen H D and Sahn D J Pediatric and Adolescent Echocardiography Chicago 1975 Year Book Medical Publishers, Inc.

Book reviews

Clinical Hypertension second edition By Norman M Kaplan M D Baltimore 1978 The Williams & Wilkins Company 40[illegible] pages Price $41 00

This book is intended for clinicians This is an excellent publication on a disease which is extremely common and important It must be treated in some manner by practically all practicing doctors Kaplan discusses clearly diagnosis and management The book is well written The dietary recommendations are presented including tables listing foods for the management of hypokalemia a constant problem when kaliuretic drugs are used The index is well organized and usable and the bibliographies though brief document statements in the text effectively The common types of hypertension are clearly defined and discussed including renovascular hypertension aldosteronism low renin hypertension and pheochromocytoma This is a good book that should interest all doctors

Cardiac Glycosides Edited by G Bodem and H J Dengler New York 1978 Springer Verlag 428 pages Price $29 00

This publication includes the discussions at an international symposium held in Bonn during January 1977 on the cardiac glycosides This series of papers summarizes very well the chemistry pharmacology and clinical use of the cardiac glycosides The metabolism and excretion of the various glycosides are discussed including the pharmacokinetics in renal disease and uremia The aspects of background knowledge concerning the cardiac glycosides are important but the clinical use of the glycosides was neglected in the symposium so that the practicing physician will find little use for this publication In fact this reviewer finds conflicts of methods for digitalizing patients The use of the digoxin blood level is relied upon by some of the participants for judging the clinical state of digitalization of patients whereas others do not This is also true in the hospitals and clinics throughout the world This publication is a good reference book The contributors [illegible] to advise the reader how to digitalize a patient satisfactorily without intoxicating him even though this can be done

Cardiac Pathology By Colin M Bloor Philadelphia 1978 J B Lippincott Company 4[illegible]0 pages Price $39 00

This is a very good book on cardiac pathology It is brief succinct and thorough. The practice of good cardiology without a knowledge of cardiac pathology is impossible Bloor's book includes discussions of the important selected problems in clinical cardiac pathology Embryology anatomy physiology and clinical manifestations are interwoven in the discussion of the pathology of congenital and acquired types of heart disease This book is written for clinicians as well as for pathologists. The illustrations are good the bibliography appended to each chapter is well selected and the publication is well done This is a good book

Clinical Echocardiography By Jacob I Haft M D and Michael S Horowitz M D, Mount Kisco New York, 1978, Futura Publishing Company Inc 248 pages, Price $19 00

Many books are appearing on the subject of echocardiography This book is another one which really adds very little new to the field Those interested in the subject will find this book can supplement others very little The discussion of the interventricular septum is interesting This is one structure in which the function is observed best by echocardiography This is a satisfactory book on echocardiography

Clinical Echocardiography By Navin C Nanda and Raymond Gramiak St Louis 1978 The C V Mosby Company 4[illegible]1 pages Price $37.[illegible]0

This is an excellent book on echocardiography The authors have contributed considerably to the development of echocardiography as a clinical diagnostic tool The presentations are authoritative and reflect a great deal of personal experience and thought The book is divided into two parts (1) fundamentals of echocardiography and (2) clinical echocardiography The latter consists of chapters concerned with each anatomic structure of the heart such as the four valves, the left ventricle prosthetic valves pericardial fluid and two-dimensional echocardiography The text is clear and the illustrations are good but do reveal the problems of obtaining excellent recordings The diagrams are extremely helpful in clarifying the two-dimensional recordings by sector scan. This is an excellent and authoritative book on echocardiography

Clinical Echocardiography Edited by Morris N Kotler and Bernard L. Segal Philadelphia 1978 F A Davis Company 301 pages Price $35.00

This is another excellent issue of *Cardiovascular Clinics* The subject is timely and deals with a rapidly developing field The many contributors have reviewed the field very well, including a discussion of training physicians and technician The sector scan is reviewed as well as many important clinical applications of echocardiography This volume should not only interest trainees in cardiology and internal medicine but physicians in general who will be using echocardiography more and more This procedure is an important new development in medicine Unfortunately some observers over read the tracings and attempt to quantitate hemodynamic phenomena while the method has not yet made accurate quantitation of most hemodynamic and cardiodynamic phenomena possible The critical reader will learn this for himself from the various discussions. Many of the indices described need to be evaluated by reliable quantitative studies and even such reliable standards are not yet available This volume is a good addition to the echocardiographic literature

Books received

Regulation of Ventilation and Gas Exchange Edited by Donald G Davies and Charles D Barnes, New York 1978, Academic Press Inc 308 pages, Price $22 00

Preventing Coronary Heart Disease By A C Artzenius F H Epstein K H Gunther M Kornitzer J Menard T Strasser and R C DeBoeck Assen The Netherlands 1978 Van Gorcum & Company B V., 66 pages

Blades Surgical Diseases of the Chest Edited by Donald Brian Effler St Louis, 1978 The C V Mosby Company 839 pages Price $59 50

Basic Cardiology for the Practicing Physician

A course entitled Basic Cardiology for the Practicing Physician will be held at the Ahwahnee in Yosemite National Park California on March 16 through 19 1980 This course is sponsored by the Department of Medicine Division of Cardiology and Extended Programs in Medical Education University of California School of Medicine San Francisco This course is designed for physicians in the fields of Family Practice General Practice and Internal Medicine to update their knowledge of current cardiology diagnostic methods through lectures and workshops with case studies. The course is approved for 15 hours of Category 1 Credit For further information please contact Extended Programs in Medical Education Room 5OU University of California Third and Parnassus Aves San Francisco Calif 94143 Telephone (415) 666-4251

Computers in Critical Care Medicine

The second international symposium on Computers in Critical Care and Pulmonary Medicine will take place in Lund Sweden from June 3 through 6 1980 Correspondence regarding abstracts, papers registration and symposium accommodations should be addressed to Miss Bodil Richardson Symposium Secretary Kliniskt Fysiologiska Avdelningen (Department of Clinical Physiology) Lasarettet S 221 85 Lund Sweden

Clinical Approach to Exercise Testing

A seminar entitled Clinical Approach to Exercise Testing will be held on April 10 through 12 1980 at the Sheraton Sand Key Hotel Clearwater Beach Fla Program directors are Stephen I Chaser M D and Pamela I Clark R N For further details contact Ms. Billie N Chiles, Tampa Tracings, P O Box 1245 Tarpon Springs, Fla 33589

Workshop in Echocardiography

A Workshop in Echocardiography will be presented on March 27 through 30 1980 at the Don Cesar Beach Resort Hotel St Peterburg Beach Fla The workshop will be directed by Louis E Teichholz M D of the Mount Sinai School of Medicine New York City For further information regarding this workshop contact Ms Billie N Chiles Tampa Tracings, P O Box 1245 Tarpon Springs Fla 33589

Tenth Heart Congress

On September 23 through 28 1980 the Tenth Heart Congress of the International Society for Heart Research will be held in Moscow U S S R For further information contact Professor V N Smirnov National Cardiology Research Center Academy of Medical Sciences Petroverigsky Lane 10 Moscow 101837 U S S R

American Heart Journal

February 1980 Volume 99 Number 2

Editorial

The complications of coronary arteriography a problem that won t go away

Steven A Schroeder M D
San Francisco Calif

Coronary arteriography may be the fastest growing major invasive procedure of the past decade For example at the Montreal Heart Institute the frequency of coronary arteriography increased from about 71 procedures per year in 1965 and 1966 to about 1 000 cases per year by 1970 In 1975 cardiac catheterization (predominantly coronary arteriography) was the most common surgical procedure reported at the University of California San Francisco hospitals occurring almost twice as frequently as the next most common procedure cesarean section

The value of this procedure undoubtedly derives from its establishment as the gold standard for the presence of coronary artery disease This combined with considerable professional disagreement concerning its indications as well as its relative ease of performance and widespread availability in the community contributes to its popularity Possible reasons for this last factor include the large number of cardiologists being trained (in 1975 1 052 cardiology certificates were awarded by the American Board of Internal Medicine accounting for 19 per cent of all certificates awarded by the Board) the increasingly aggressive approach to coronary artery disease and financial incentives for the performance of surgical rather than medical care

Along with the obvious and well touted benefits of coronary arteriography however are a set of associated risks Since these have been summarized in several excellent reviews [1-5] a detailed summary will not be attempted here except to emphasize two points First substantial variability exists in mortality and morbidity rates among different catheterization laboratories for example published mortality rates range from as low as 0 1 per cent to one extraordinary case of an institution with a reported rate of 8 per cent Second rates of catheter associated deaths and severe complications do not appear to be decreasing Factors associated with increased risks of mortality and morbidity include use of the femoral as opposed to the brachial artery approach inexperience of the operator and/or the laboratory low volume of cases performed at the laboratory presence of associated diseases especially significant stenosis of the left main coronary artery long and complex procedures and absence of systemic heparin given to prevent thromboembolic complications In reviewing these data Judkins and Gander suggest that laboratories with death rates in excess of 0 3 per cent should stop doing procedures altogether and reassess program goals and commitments

It was because of concern about the risks of invasive diagnostic procedures that Drs Keith Marton Brian Strom and I recently undertook a small pilot study of their frequency and complication rates on all patients of the medical services of two university hospitals The results published in the December 1978 *Archives of Internal Medi*

From the Health Policy Program School of Medicine University of California San Francisco

Received for publication Feb 13, 1979

Reprint requests Steven A Schroeder M D Health Policy Program School of Medicine University of California San Francisco 1326 Third Ave San Francisco Calif 94143.

0002 8703/80/020139 + 03$00 30/0

cine showed that in the period studied invasive procedures were commonly performed 47 per cent of the 303 patients admitted to the two services underwent at least one invasive procedure and each of these had an average of 1 6 such procedures The most frequent procedure was catheterization of the left side of the heart occurring in 34 patients Nineteen of these procedures were coronary arteriograms and most also included right sided catheterization Lumbar puncture was the second most common procedure occurring in 31 patients Catheterization limited to the right side of the heart ranked sixth with 12 cases Altogether cardiac catheterization accounted for 20 per cent of all invasive procedures performed in the study

Twenty nine complications of procedures were recorded in 20 patients The largest number of complications resulted from left sided catheterization totalling ten incidents in six patients Fortunately these were relatively minor including hemorrhage (three patients) fever (two patients) and arrhythmia hypotension phlebitis pulmonary edema and psychological trauma (one case each) The complication of psychological trauma refers to a patient who deferred needed valvular surgery because of anxiety generated by treatment of post catheterization hypotension Although no deaths were recorded three of the complications required specific therapy uch as blood transfusion and six required thera y as well as prolonged hospitalization During the time period studied a patient undergoing left sided cardiac catheterization had a 16 per cent chance of having a complication that required therapy and/or prolonged hospitalization None of the evere complications that can result from the procedure such as systemic emboli loss of limb myocardial infarction or perforation occurred

While the frequency of minor nonfatal complications in our small study is higher than in the published literature we believe that the published incidence of complications may be misleadingly low To begin with in titutions with high complication rates do not usually report their experience thereby making generalizations from the published literature unreliable Reports that are published contain at least three important biases The first is that multi institutional surveys may under represent hospitals with more frequent complications For example the survey of 313 coronary arteriography laboratories by Adams Fraser and Abrams only received results from 46 per cent of the institutions contacted The second bias is that routine reporting underestimates complication rates For example careful studies of hospital infections show actual infection rates that are two or three times greater than those routinely reported [11] The third bias derives from the short observation period during which complications are sought thus excluding late complications such as post transfusion hepatitis

Five years ago Judkins and Gander concluded that the high reported rates of complications of coronary arteriography are unacceptable [12] There are at least four different strategies that could help make these risks more acceptable First there should be routine and accurate surveillance of complication rates including mortality at all laboratories performing coronary arteriography These data should be analyzed periodically and should be readily available to all physicians and patients (If the laboratory can provide stratified risks according to clinical conditions such as age or presence of left main disease the data will be that much more meaningful It should be remembered however that the lowest complication rates are likely to occur in perfectly healthy patients) Each laboratory should determine ahead of time the level at which complication rates are unacceptable and be prepared to consider a set of corrective actions including closing the laboratory This individual laboratory surveillance effort must also be supplemented by coordinated national programs Surveys such as the one by Adams Fraser and Abrams should be repeated periodically hopefully with a greater than 46 per cent participation rate Better still would be a system of periodic national surveillance conducted by a national agency such as the Center for Disease Control in Atlanta Georgia Such a model already exists for nosocomial infection surveillance

Second if periodic surveys continue to show some laboratories with unacceptably high fatality and complication rates (adjusted for disease severity and age) strategies either to improve or close down those laboratories should be available For example malpractice premiums could be adjusted to reflect actual complication rates there could be enforcement of minimal resources for catheter laboratories along the lines of the Report of the Inter Society Commission for

Heart Disease Resources and performance criteria of catheterization laboratories could be included as part of hospital accreditation procedures

Third attempts should be continued to achieve a professional consensus regarding *indications* for the procedure The Report of the Ad Hoc Committee on the Indications for Coronary Arteriography is one such attempt However subsequent reviews of coronary arteriography have continued to present extremely broad indications for the procedure including for example the need to know as an indication considered apart from the likelihood of subsequent operative intervention

Fourth the risks of coronary arteriography need to be emphasized more in the current medical literature In Hurst s recent 2 000 page text on heart disease only one half page is devoted to complications of coronary arteriography and no risk figures are provided Grossman s standard text on *Cardiac Catheterization and Angiography* mentions the major complications of coronary arteriography but concludes that fortunately the incidence is low

Given that most physicians are reluctant to prescribe drugs such as chloramphenicol that carry a risk of fatal reaction of approximately one in 40 000 it is hard to agree that fatality rates ranging from one per thousand to 80 per thousand are low Coronary arteriography is clearly one of the reasons that cardiology has entered into a golden age during the past two decades Nevertheless there must be greater awareness of the procedure s associated risks and wider knowledge of the extent of those risks at each institution Availability of such data will at the very least enhance clinical decision making clarify benefit risk issues and offer legal protection It might even lead to a decrease in the rate of complications of coronary arteriography

REFERENCES

1. Bourassa M G and Noble J Complication rate of coronary arteriography A review of 5250 cases studied by a percutaneous femoral technique Circulation 53 106 1976
2. Schroeder S A and Showstack J A The dynamics of medical technology use Analysis and policy options *in* Medical Technologies The Culprit Behind Health Care Costs? proceedings of the 1977 Sun Valley Forum Altman S and Blendon R editors (In press)
3. Braunwald E Deaths related to cardiac catheterization Circulation (Suppl III) 17 1968
4. Selzer A Anderson W L and March H W Indications for coronary arteriography Calif Med 115 1 1971
5. Adams D F Fraser D B and Abrams, H L The complications of coronary arteriography Circulation 48 609 1973
6. Takaro T Hultgren H N Littman D, Wright E C and Oteen N C An analysis of deaths occurring in association with coronary arteriography Am Heart J 86 587 1973
7. Judkins M P, and Gander M P Prevention of complications of coronary arteriography Circulation 49 599 1974
8. Takaro T Hultgren H N and Detre K M An assessment of risks and causes of death in association with coronary arteriography *in* Coronary Artery Medicine and Surgery Concepts and Controversies New York 1975 Appleton Century Crofts pp 228-236
9. Wolfson S Grant D Ross A M, and Cohen L S Risk of death related to coronary arteriography Role of left coronary arterial lesions Am J Cardiol. 37 210 1976
10. Schroeder S A Marton K I and Strom B L Frequency and morbidity of invasive procedures Report of a pilot study from two teaching hospitals Arch. Intern Med 138 1809 1978
11. Eickhoff T C Brachman P, Bennett J V and Brown J F Surveillance of nosocomial infections in community hospitals I Surveillance methods, effectiveness and initial results J Infect Dis 120 305 1969
12. Judkins M P Abrams, H L Bristow J D Carlsson E Criley J M Elliot L P Ellis K B Friesinger G C, Greenspan R H and Viamonte M Report of the Inter Society Commission for Heart Disease Resources Optimal resources for examination of the chest and cardiovascular system Circulation 53 A1 1976.
13. Bristow J D, Burchell, H B Campbell, R W Ebert, P A, Hall R J Leonard J J and Reeves T J Report of the ad hoc committee on the indications for coronary arteriography Circulation 55 969A 1977
14. McIntosh H D Indications for coronary arteriography Circulation 56 1 1977
15. Conti C R Coronary arteriography Circulation 55 227 1977
16. Hurst J W The Heart New York 1978 McGraw Hill Book Company Inc
17. Grossman W Cardiac Catheterization and Angiography Philadelphia 1974 Lea & Febiger
18. Weinstein L Antimicrobial agents tetracyclines and chloramphenicol *in* The Pharmacological Basis of Therapeutics Goodman L S Gilman A editors, New York 1975 MacMillan Publishing Co Inc., pp 1195-1196
19. Braunwald E The first 20 years of the *American Journal of Cardiology* A chronicle of the golden age of cardiology Am J Cardiol. 42 5 1978

Frequency and direction of interatrial shunting in valvular pulmonic stenosis with intact ventricular septum and without left ventricular inflow or outflow obstruction

An analysis of 127 patients treated by valvulotomy

William C Roberts MD
Richard J Shemin MD
Kenneth M Kent MD
Bethesda Md

It is well recognized that patients with valvular pulmonic stenosis with intact ventricular septum often have shunts at the atrial level Although right to left shunting at the atrial level in these patients has received considerable attention relatively little attention has been directed toward the patients with pulmonic stenosis with left to-right interatrial shunts In this report the frequency and direction of atrial shunting is described in 127 patients who underwent pulmonic valvulotomy unassociated with ventricular septal defect Characteristics of the patients with left to right interatrial shunts are compared to those of the patients with right to left interatrial *shunts and the mechanism of the shunting is* discussed

Patients studied and findings

The records of patients undergoing operation in the National Heart Institute from 19,5 through 1977 were reviewed A total of 127 patients with valvular pulmonic stenosis with intact ventricular septum and without obstruction to left ventricular inflow or outflow or with associated aortopulmonary arterial communication underwent operative relief of the valvular obstruction during this period Of the 127 patients 9) (76%) had no shunt at the atrial level detected preoperatively at cardiac catheterization by indicator dilution curves and no defect in the atrial septum was found in them at operation Each of the remaining 31 patients (2)%) had a defect in the atrial septum found at operation and a shunt at the atrial level had been detected preoperatively by dye dilution curves (with injection of cardiogreen into the inferior vena cava and into the main pulmonary artery) in 30 (97%) of them. Statistical methods used were Student's t test of significance for differences between two groups (patients with right to left shunts vs those with left to right shunts) or paired data (comparison of two pressure measurements within individual patients in a group) Data are expressed as mean ± standard error of mean

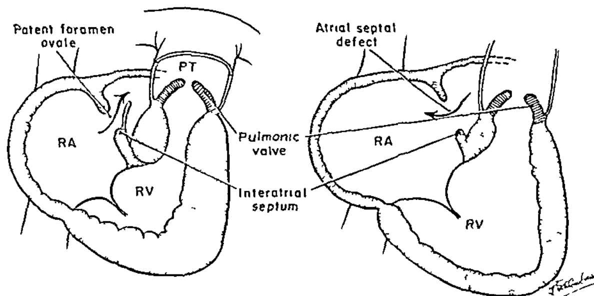
These 30 patients were divided into two major groups determined by the direction of the shunt at the atrial level 19 patients with right to-left shunts (four of them [patients BB LP TR and CC Table I] also had minute left to right shunts by pulmonary arterial dye curves) and 11 patients with left to right shunts and no evidence of right to left shunting Clinical hemodynamic and operative observations in each of the 30 patients is detailed in Table I

The 19 patients with right to left shunts compared to the 11 patients with left to right shunts tended to be *older* (average age 18 vs 14 years)

From the Pathology Surgery and [illegible] National Heart, Lung, and Blood Institute [illegible] Health Bethesda, Md.

Received for publication Jan. 5 1979
Accepted for publication Oct.19 1979

Reprint requests William C Roberts MD [illegible] National Institutes of Health, Bethesda, Md. [illegible]



Right-to-Left Shunt Severe Pulmonic Stenosis and Patent Foramen Ovale

Left-to-Right Shunt Moderate Pulmonic Stenosis and True Atrial Septal Defect

Fig 1 Diagram displaying the essential differences between patients with pulmonic stenosis and right to left interatrial shunts and those with left to-right interatrial shunts The former produces primarily a *pressure overload* right ventricular type heart and the latter a *volume overload* right ventricular type heart

and had higher average *blood hematocrit* levels (51 vs 42) *but neither of these were statistically* significant The *systemic arterial oxygen saturation* was less in the patients with right to left shunting (85 ± 2 vs 93 ± 1 $p < 0.05$) The patients with right to left shunting had lower *systolic pulmonary arterial pressures* (13 ± 1 vs 20 ± 1 mm Hg $p < 0.001$) but *diastolic pressures* were similar (6 ± 5 vs 9 ± 1 mm Hg NS) *Right ventricular systolic pressures* were greater in the patients with right to left shunts (136 ± 10 vs 80 ± 5 mm Hg $p < 0.001$) but *right ventricular diastolic pressures* were similar (7 vs 8 mm Hg NS) The *peak systolic pressure gradients between right ventricle and pulmonary trunk* were greater in the group with right to left shunts (120 ± 11 vs 60 ± 5 $p < 0.001$) *Right atrial a* (9 ± 1 vs 8 ± mm Hg NS) and *v waves* (5 ± 0.5 vs 5 ± 1 mm Hg NS) were similar in the two groups but *mean right atrial pressures* was less in the group with right to left shunts (4 ± vs 5 ± 0.5 mm Hg $p < 0.01$) The *defects in the atrial septum* were much smaller (average 1.1 ± 0.1 cm in diameter) in the 19 patients with right to left shunts than in the 11 patients with *left to right shunts* (average 2.8 ± 0.1 cm in diameter) This difference in size of the interatrial defect in the two groups of patients is further emphasized by the method chosen to close the defect at operation in 16 (84%) of the 19 patients with right to left shunts and in only two (18%) of the 11 patients with left to right shunts the defect in the atrial septum was closed by suture alone indicating that the defect in these 18 patients (60% of the total of 30 patients valvular pulmonic stenosis and atrial shunts) was small and simply a patent foramen ovale In contrast in only three (16%) *of the* 19 patients with right to left shunts and in nine (82%) *of the 11* patients with left to right shunts the defect in the atrial septum was closed by a patch indicating that these defects were large and therefore not a simple patent foramen ovale but a true atrial septal defect or at least a severely stretched membrane of the fossa ovale

As shown in Table I comparison of the right and left atrial pressures in the patients with right to left shunts showed little to no di ce

Table I Observations in each of 30 patients with valvular pulmonic stenosis and interatrial shunts

Pt	Age (yrs)	Sex	SA Hct (%)	SA O_2 Sat (%)	Pressures (mm Hg) PA s	PA d	RV s	RV d	RV-PA psg	RA a	RA v	RA m	LA a	LA v	LA m
Right to left shunt															
RR	3	M	47	8[illegible]	10	6	100	8	90	10	6	[illegible]	8	6	[illegible]
CI	4	F	41	8[illegible]	10	[illegible]	110	[illegible]	100	10	4	5	10	3	4
EP	4	F	48	88	—	—	1[illegible]5	10	—	—	—	—	8	4	5
MC	5	F	4[illegible]	8[illegible]	[illegible]	4	8[illegible]	4	[illegible]8	4	0	2	4	0	[illegible]
KM	[illegible]	F	42	91	—	—	120	7	—	8	[illegible]	4	8	6	5
DJ	6	F	42	93	10	7	10[illegible]	3	9[illegible]	4	4	2	[illegible]	9	3
JW	7	M	51	80	12	6	100	[illegible]	89	—	—	4	—	—	—
CC	9	F	60	8[illegible]	18	[illegible]	118	5	100	4	7	4	5	[illegible]	4
BB	11	F	42	[illegible]	—	—	13[illegible]	5	—	—	—	5	—	—	[illegible]
DP	13	M	49	84	24	12	1[illegible]	1[illegible]	1[illegible]	1[illegible]	10	6	—	—	6
TR	15	F	49	93	18	9	210	10	222	9	6	5	9	[illegible]	3
LI	20	F	60	68	12	4	192	8	180	10	6	5	—	—	—
CL	24	F	54	[illegible]	—	—	168	6	—	6	4	2	9	3	[illegible]
FS	2[illegible]	F	[illegible]	82	1[illegible]	10	16[illegible]	0	1[illegible]0	9	1	4	8	0	4
SR	28	F	61	[illegible]	9	[illegible]	143	5	134	8	6	2	9	5	5
RW	34	M	4[illegible]	91	1[illegible]	4	[illegible]0	4	55	11	5	4	—	—	—
SM	3[illegible]	M	4[illegible]	93	12	6	[illegible]8	6	6[illegible]	9	[illegible]	4	9	[illegible]	6
VD	40	F	62	8[illegible]	12	6	1[illegible]2	1[illegible]	140	9	3	4	—	—	—
AN	43	F	[illegible]	84	12	8	182	1[illegible]	1[illegible]0	12	3	4	—	—	—
Totals	18 ± 3		51 ± 2	8[illegible] ± 2	13 ± 1	6 ± 0.[illegible]	13[illegible] ± 10	[illegible] ± 1	1[illegible]0 ± 11	9 ± 1	5 ± 0.5	4 ± 0.[illegible]	8 ± 0.[illegible]	5 ± 1	4 ± 0.[illegible]
Left to right shunt															
ST	4	F	43	93	28	8	115	1[illegible]	8	1[illegible]	8	8	1[illegible]	10	8
JS	6	M	44	92	18	8	[illegible]	6	[illegible]	5	4	3	—	—	—
LZ	6	F	3[illegible]	88	24	14	68	1[illegible]	4[illegible]	4	0	2	8	3	5
RL	8	F	41	94	24	12	[illegible]0	10	44	9	[illegible]	5	11	9	8
JH	11	F	41	91	15	8	[illegible]0	0	5[illegible]	[illegible]	2	5	12	0	[illegible]
JK	13	M	42	93	1[illegible]		60	5	4	10	3	6	11	1	[illegible]
RS	1	M	4[illegible]	94	20	8	80	8	60	11	[illegible]	[illegible]	14	12	6
WP	1[illegible]	M	43	[illegible]	12	3	[illegible]8	6	6[illegible]	—	—	[illegible]	—	—	6
RR	19	F	3[illegible]	92	22	16	110	13	88	10	7	8	16	14	10
RR	2[illegible]	F	42	9[illegible]	22	8	6[illegible]	10	43	10	9	8	—	—	8
CC	28	F	41	93	18	6	82	4	64	6	4	2	5	5	4
Total	14 ± 3		4[illegible] ±	93 ± 1	20 ± 1	9 ± 1	80 ± 5	8 ± 1	60 ± 5	8 ± 1	5 ± 1	5 ± 0.5	11 ± 1	[illegible] ± 1	[illegible] ± 0.5
	NS		NS			NS		NS		NS	NS			NS	

Abbreviations a = a wa ASD = atrial septal defect d = end-diastole Hct = hematocrit m = m n f = patch PA = pulmonary artery psg = pe k lo pressure qP qS = pulmonary systemic flow ratio RA = right atrium RV = right entricle s = pe k s le Su = utum SA = stemic artery S = sat ati n SV = temic ein = wa e
p < 0.0

despite a small defect in the atrial septum In contrast with the exception of one patient in those with left to right interatrial shunts the left atrial pressures were higher than the right atrial pressures despite the presence of a relatively large defect in the atrial septum Among the eight patients with left to right interatrial shunts in whom the a v and mean pressures were recorded from both atria the right atrial and their corresponding average left atrial pressures were as follows a = 8 ± 1 and 11 ± 1 mm Hg ($p < 0.01$) v = 5 ± 1 and 7 ± mm Hg (NS) and mean = 5 ± 0.5 and 7 ± 0.5 mm Hg ($p < 0.01$) Among the 11 patients with right to left interatrial shunts these corresponding average pressures were as follows a = 9 ± 1 and 8 ± 0.5 mm Hg (NS) v = 5 ± 0.5 and 5 ± 1 mm Hg (NS) and mean = 4 ± 0.5 and 4 ± 0.5 mm Hg (NS)

The right ventricular end diastolic pressures tended to be lower than the left ventricular end diastolic pressures in the patients with right to left interatrial shunts but this difference was not statistically significant In the patients with exclusive left to right shunts left ventricular

LV s	d	qP/qS	Size (cm) ASD	Closure ASD by
—	—	—	1 0	Su
100	5	—	1.5	Su
—	—	—	1 0	Su
105	5	—	1 0	Su
—	—	—	0 8	Su
107	9	—	1 0	Su
105	8	—	2.2	I
100	4	—	1 5	Su
145	7	—	1 0	Su
—	—	—	1 5	P
96	6	—	1 0	Su
—	—	—	1 0	Su
—	—	—	1 0	P
120	0	—	1 0	Su
117	7	—	1.5	Su
—	—	—	1.0	Su
—	—	—	1 0	Su
—	—	—	1 0	Su
—	—	—	0 7	Su
110 ± 5	6 ± 1		1 1 ± 0 1	
129	12	1 1	2 0	P
—	—	1 4	—	P
115	10	—	5 0	I
—	—	1 3	1.5	Su
125	0	1.8	2 5	P
120	2	—	2.5	P
122	12	1 4	3 0	P
138	6	1 6	3 0	P
135	0	1 5	1.5	Su
—	—	1.8	3 0	P
80	6	1 2	4 0	P
121 ± 6	6 ± 1		2 8 ± 0 1	
NS	NS			

end diastolic pressures tended to be lower but not significantly different. Of the nine patients with right to left shunts in whom both right and left ventricular end diastolic pressures were recorded, the right averaged 7 ± 1 and the left 6 ± 1 mm Hg (NS). Of the eight patients with exclusive left to right shunts in whom both right and left ventricular end diastolic pressures were recorded, the right averaged 8 ± 1 and the left 6 ± 1 mm Hg (NS).

In addition to searching the operative records for patients with valvular pulmonic stenosis with intact ventricular septum, the records of patients with closure of atrial septal defect without ventricular septal defect also were examined. A total of 436 patients underwent operative closure of atrial septal defect (excluding ostium primum type) at the National Heart Institute from 1955 through 1977. Of this number, 31 (7%) (included above) had valvular pulmonic stenosis with normally functioning left sided cardiac valves and all underwent valvulotomy.

Comments

The above observations in patients with congenital valvular pulmonic stenosis without ventricular septal defect or left ventricular inflow or outflow obstruction indicate that shunting at the atrial level is fairly common and that the shunting is more commonly right to left than left to right. Among our 127 patients with isolated pulmonic stenosis, 30 (24%) had shunts detected preoperatively by indicator dilution curves at the atrial level: in 19 (63%) the shunt was exclusively or nearly so right to left (hereafter called "right to left") and in the other 11 (37%) the shunt was entirely left to right (hereafter called "left to right"). In all 19 patients with right to left shunts detected at cardiac catheterization, a defect at the atrial level had been suspected clinically because of central cyanosis either at rest or with exertion or both. Of the 11 patients with left to right shunts, no shunting at this level was suspected before cardiac catheterization in 4, and an atrial septal defect was suspected in 7. In 10 of the latter 11 patients, pulmonic valve stenosis was diagnosed clinically before cardiac catheterization, and in the remaining one patient atrial septal defect was the only pre catheterization diagnosis. All 11 patients were acyanotic even with strenuous exertion. Whereas none of the 19 patients with right to left shunts had wide splitting of the second heart sound at the cardiac base by auscultation (most had single second heart sounds in this area), six of the 11 with left to right shunts had wide if not fixed splitting of the second heart sound by either auscultation or phonocardiography or both.

The explanation for the differing direction of the shunting at the atrial level in the 30 patients appears to be the *size of the defect in the atrial septum and the degree of obstruction to right ventricular outflow*. With one exception, the defect in the atrial septum was small (average = 1 1 cm) in each of the 19 patients with

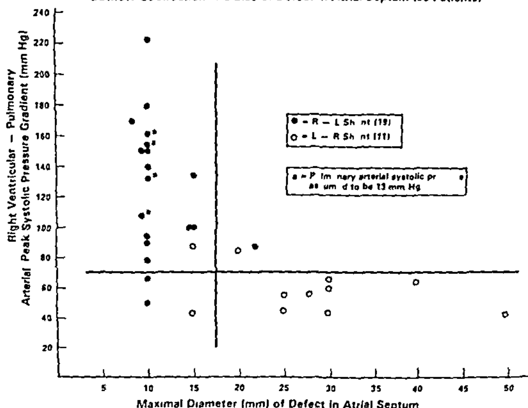


Fig 2 Relation between the degree of the right ventricular outflow obstruction and the size of the defect in the atrial septum is shown

right to left shunts and as determined from descriptions of the atrial septum at operation was simply a patent foramen ovale Because the membrane of the fossa ovale is located on the left side of the atrial septum higher pressures on the right than on the left side of the atrial septum appear to be responsible for the shunts being right to left in the presence of a simple patent foramen ovale If the foramen ovale is patent but valvular competent exclusive left to right shunting at the atrial level is impossible even if the left atrial pressures are considerably higher than the right atrial pressures because the membrane in this circumstance simply will be pressed against the septum not away from it Among the 19 patients with right to left shunting at the atrial level however no significant differences in the pressures (a wave v wave and mean) in the right atrium compared to their respective counterparts in the left atrium were observed (Table I) The usual explanation for right to left shunts occurring in the presence of right ventricular pressure overload is a decrease in right ventricular compliance Of course no measurement of ventricular compliance was made but neither right atrial nor right ventricular end diastolic pressure was greater than their corresponding pressure on the left side

The explanation for the left to right shunts at the atrial level in the other 11 patients appears to reside at least in part in the *relatively large size* (avg 2 8 cm in diameter) *of the defect in the atrial septum* Of these 11 patients the defect in the atrial septum was closed by a patch in nine whereas a patch was utilized for closure in only three of the 19 patients with right to left shunts Among the eight recorded the left atrial pressures including a and v waves and mean pressures were higher in the left atrium than their respective counterparts in the right atrium Although in five of the eight patients recorded the left ventricular end diastolic pressure was equal to or higher than the right ventricular end diastolic pressure the average left ventricular end diastolic pressure was lower than the average right ventricular end diastolic pressure (6 0 vs 7 2 mm Hg)

Another major hemodynamic difference be

tween the patients with right to left shunts and those with left to right shunts at the atrial level was the *magnitude of the obstruction to right ventricular outflow* The 19 patients with right to left shunts had right ventricular to pulmonary arterial peak systolic pressure gradients twice as high as did the 11 patients with left to right shunts (120 vs 60 mm Hg) Accordingly the right ventricular systolic pressures were nearly twice as high in the patients with right to left shunts compared to those with left to right shunts (136 vs 80 mm Hg) but the right ventricular end diastolic pressures in the two groups were similar (8 and 7 mm Hg respectively)

Although numerous reports ' have emphasized the frequency of right to left shunting at the atrial level in patients with isolated pulmonic stenosis relatively few have focused on patients with exclusive left to right shunting at the atrial level The first to do so appears to have been Abrahams and Wood in 1951 These authors described clinical observations in 52 patients with isolated pulmonic stenosis 37 of whom had intact atrial septa and 15 of whom had defects in the atrial septum In eight of the latter 15 patients the shunt at the atrial level was right to left and all of them had evidence of *severe* pulmonic valve obstruction The other seven had evidence of left to right shunting at the atrial level and all had only *mild* pulmonic stenosis Abrahams and Wood reasoned that the patient with a venoarterial interatrial shunt had a patent foramen ovale and that the patient with an arteriovenous interatrial shunt had a true atrial septal defect Anatomic confirmation of this reasoning however was not available Deughar and Zak described predominant left to right shunting at the atrial level in one of their four patients with isolated pulmonic stenosis Broadbent and associates observed five patients with isolated pulmonic stenosis and left to right shunting at the atrial level and pointed out that the right ventricular outflow obstruction was mild in four (peak systolic pressure gradients from 22 to 35 mm Hg) and severe in only one (peak systolic pressure gradient = 122 mm Hg) Again none of their five patients had undergone cardiac operation or necropsy Moffitt and associates described two patients with isolated pulmonic stenosis and left to right interatrial shunting the degree of right ventricular outflow obstruction in each was mild (gradients 25 and 29 mm Hg respectively) Few subsequent reports have emphasized or discussed mechanisms of left to right shunting at the atrial level in patients with isolated pulmonic stenosis

In conclusion patients with isolated pulmonic stenosis and right to left interatrial shunts usually have *small defects in the atrial septum* (patent foramen ovale) and *severe pulmonic stenosis* Patients with isolated pulmonic stenosis and left to right interatrial shunts usually have relatively *large defects in the atrial septum* (true atrial septal defect) and *mild to moderate obstruction to right ventricular outflow*

Summary

This report summarizes observations in 127 patients who underwent pulmonic valvulotomy for valvular pulmonic stenosis with intact ventricular septum and without obstruction to left ventricular inflow or outflow Of the 127 patients 30 (24%) preoperatively by dye dilution curves had shunting at the atrial level in 19 (63%) the shunt was right to left and in the other 11 (27%) entirely left to right The patients with right to left interatrial shunts had severe pulmonic valve stenosis (average peak systolic pressure gradient = 120 ± 11 mm Hg) and small (average diameter 1 1 ± 0 1 cm) sized defects in the atrial septum (patent foramen ovale) In contrast the patients with left to right shunts had mild to moderate pulmonic valve stenosis (average peak systolic pressure gradient = 60 ± 5 mm Hg) and relatively large (average diameter = 2 8 ± 0 1 cm) defects in the atrial septum (true atrial septal defect) The patients with right to left interatrial shunts had no significant differences in right versus left atrial pressures The patients with left to right interatrial shunts however had left atrial pressures significantly greater than right atrial pressures (7 ± 0 5 vs 5 ± 0 5 p < 0 05) No significant differences were found in ventricular end diastolic pressures

REFERENCES

1 Selzer A Carnes W H Noble C Jr Higgins W H Jr and Holmes R O The syndrome of pulmonary stenosis with patent foramen ovale Am J Med. 6 3 1949

2 Engle M A and Taussig H B Valvular pulmonic stenosis with intact ventricular septum and patent foramen ovale Report of illustrative cases and analysis of clinical syndrome Circulation 2 481 1950

3 Maraist F Daley R Draper A Jr Heimbecker R Dammann F Jr Kieffer R Jr., King J T Ferencz, C., and Bing R J Physiologic studies in congenital heart disease X The physiological findings in thir

patients with isolated pulmonary valvular stenosis Bull. John Hopkins Hosp 88 1 1951
4 Calazel L, Gerald R Dales R Draper A Foster J and Bing R J Physiological studies in congenital heart disease VI A comparison of the right and left auricular capillary and pulmonary artery pressure in nine patients with auricular septal defect Bull Johns Hopkins Hosp 88 20 1951
5 Johnson R L, and Johnson F F Congenital pulmonic stenosis with open foramen ovale in infancy Report of five proved cases, AM HEART J 44 344 1952
6 Campbell M Simple pulmonary stenosis Pulmonary valvular stenosis with a closed ventricular septum Br Heart J 16 273 1954
7 Callahan J A Brandenburg R O and Swan H J C Pulmonary stenosis and interatrial communication with cyanosis Hemodynamic and clinical study of ten patients Am J Med 19 189 1955
8 Silverman B K, Nadas A S, Wittenborg M H Goddale W T and Cross R E Pulmonary stenosis with intact ventricular septum Correlation of clinical and physiologic data with review of operative result Am J Med 20 53 1956
9 Hosier D M Fitts J L and Taussig H B Results of valvulotomy for valvular pulmonary stenosis with intact ventricular septum Analysis of sixty nine patients Circulation 14 9 1956
10 Rowe R D, Mitchell S C Keith J D Mustard W T and Barnes, W T Severe valvular pulmonary stenosis with normal aortic root Immediate results of transarterial valvulotomy with notes on the clinical assessment of patient before and after operation Can Med Assoc J 78 311 1958
11 Engle M A Ito T and Goldberg H I The fate of the patient with pulmonic stenosis Circulation 30 554 1964
12 Tandon R Nada A S and Gross R E Results of open heart surgery in patients with pulmonic stenosis and intact ventricular septum A report of 108 cases Circulation 31 190 1965
13 Moller J H and Adams P Jr The natural history of pulmonary valvular stenosis. Serial cardiac catheterizations in 21 children Am J Cardiol 16 654 1965
14 Levine O R, and Blumenthal S Pulmonic stenosis Circulation 31 and 32 (Suppl III) 33 III 1965
15 Johnson L W Grossman W Dalen J E and Dexter L Pulmonic stenosis in the adult Long term follow up results N Engl J Med 287 1159 1972
16 Moody M R The natural history of uncomplicated valvular pulmonic stenosis AM HEART J 90 31 1975
17 Danilowicz D, Hoffman J I E and Rudolph, A M Serial studies of pulmonary stenosis in infancy and childhood Br Heart J 37 808 1975
18 Nakazawa M, Marks, R A Isabel-Jones J and Jarmakani, J M Right and left ventricular volume characteristics in children with pulmonary stenosis and intact ventricular septum Circulation 53 884 1976
19 Nugent E W Freedom R M Nora J J, Ellison, R C Rowe R D, and Nadas A S Clinical course in pulmonary stenosis, Circulation 55 and 56 (Suppl I) I 1977
20 Abrahams D C, and Wood P Pulmonary stenosis with normal aortic root Br Heart J 13 19 1951
21 Deughar D C, and Zak G A Cardiac catheterization in congenital heart disease I Four cases of pulmonary stenosis with increased pulmonary blood flow Guys Hosp Reports 101 1 1952
22 Broadbent J C, Wood E H and Burchell, H B Left to right intracardiac shunts in the presence of pulmonary stenosis Proc Staff Meetings Mayo Clin 28 101 1953
23 Moffitt G R Jr Zinsser H F Jr Kuo P T Johnson, J, and Schnabel, T C, Jr Pulmonary stenosis with left to right intracardiac shunts Am J Med 16 521 1954
24 Magidson O Cosby R S Dimitroff S P, Levinson D C and Griffith, G C Pulmonary stenosis with left to right shunt Am J Med 17 311 1954

Serial myoglobin vs CPK analysis as an indicator of uncomplicated myocardial infarction size and its use in assessing early infarct extension

Carl L Tommaso M D
Ken Salzeider M D
Mohammed Arif M D
William Klutz M D
Chicago Ill

An assay for the presence of myoglobin in urine or serum has been available for many years and has been used as a marker for the presence of myocardial necrosis As has been previously noted release of myoglobin from myocardial cells probably only occurs after irreversible cellular necrosis However the inability to distinguish myocardial from skeletal myoglobin limits its specificity as a clinical tool Myoglobin does have the distinction of being one of the first biochemical markers of myocardial damage to appear in the serum and is one of the most rapidly cleared Hence fluctuations in serum myoglobin content should separate episodes of necrosis occurring during the course of a documented acute infarction Indeed Kagen and associates have shown a staccato phenomenon of myoglobin release suggesting that a myocardial infarction is a series of separately occurring episodes of necrosis

Unlike the other biochemical markers which are cleared through the reticulo endothelial system myoglobin is cleared through the kidney In addition it has been shown that myoglobin is metabolized by the kidneys as well making renal function and renal blood flow very important in determining serum levels Hence changes in cardiac output and renal perfusion during acute infarction may affect myoglobin clearance and serum levels We therefore chose patients with normal renal function and hemodynamically uncomplicated infarction to study the appearance and clearance characteristics of myoglobin to assess the use of myoglobin as an indicator of the size of an infarct and to determine if myoglobin can identify the progression or extension of myocardial necrosis

Methods

Patients were evaluated upon arrival at the emergency room and were considered for inclusion if the clinical event had occurred and a diagnostic electrocardiogram had been recorded within the previous six hours They were excluded if renal function as determined by serum creatinine was abnormal if other significant illness was present or if they gave a history of a previous infarction strenuous activity in the preceding 24 hours recent intramuscular injections or cardioversion From all patients entered those who remained in Killip Class I for the duration of their Coronary Care Unit (CCU) stay (n = 8) form the basis for this study

All events were timed from the initial onset of chest pain or symptoms that brought the patients

From th Department f Med cin and N clear Medicine Rog r Williams Gen al Ho pit l Brown Uni ersity Provid ce R I and th D p rtm nt f Cardiol gy Northwe t rn Uni rsity Chi o Ill.

Rec i ed for p bli tion Jun 4 19 9

Accepted fo publ cat on O t 16 19 9

R print equests Dr C rl L T mm so Divis on of Card logy Northwestern Memorial Hosp tal, 250 East S perior Street Ch c g Ill. 60611

Table I Characteristics of myoglobin appearance and clearance following an acute myocardial infarction

Patient no	Age	Infarct location	Myoglobin						
			Peak (ng/ml)	Symptom to peak (hrs)	Symptoms to elevation (hrs)	Duration of elevation (hrs)	Serum half life (hrs)	Infarct size myo ng hrs/ml	Infarct size CPK gm Eq
1	59	Inf post	185	9		21	10	22.6	11.[illegible]
2	57	Ant-sep	250	7	4	34	12	34.1	13.9
3	60	Inf	255	4	3	18	4	19.3	8.1
4	64	Inf	1225	9	4	34	5	76.1	37.1
5	34	Ant-sep	1200	4	4	17	4	83.9	44.3
6	59	Inf	370	10	4	24	7	58.3	31.4
7	53	Inf lat	415	6	4	24	7	29.8	25.0
8	56	Inf	208	6	3	14	6	12.4	6
Mean	55.3		511	6.9	3.5	23.6	7.4	40.6	21.8
SD	9.2		440	2.3	0.64	7.4	2.8	26.1	13.4

Inf = inferior Post = posterior Ant = anterior Sep = septal Lat = lateral

to the hospital While in the CCU the patients were examined daily by one of the investigators Note was made of time of any chest pain after admission

Blood was sampled in the emergency room and upon arrival in the CCU and then every three hours for at least the first 30 hours (in some cases longer) and then every five hours for a total of 50 hours after CCU admission The blood was drawn through an indwelling heparin lock and was spun separated and frozen for later analysis

The serum was analyzed for CPK (total) levels using the automated analyzer modification of the Rosalki assay and acute infarct size was determined using previously described methods at Washington University in the laboratory of Dr Robert Roberts The serum was also analyzed for its myoglobin content by radioimmunoassay using a kit from Nuclear Medical Systems Inc Newport Beach, Calif These samples were analyzed in duplicate Values varied by less than 5% and the mean value was reported The results were displayed by graph of myoglobin concentration in ng/ml vs time

An index of infarction size was hand-calculated by measuring the area under the myoglobin concentration time plot assuming baseline to be the steady state levels of normal value once the levels returned to within normal range Myoglobin half life was determined by analysis of the plot of logarithm of myoglobin concentration vs time

The data were analyzed using linear regression analysis and all values are reported as mean ± standard deviations

Results

Patient profile Of the eight patients eligible for this study there were five male and three females. In all patients infarction was confirmed by electrocardiographic evolution enzymes (typical profile of LDH SGOT and presence of CPK MB) and in the four cases where performed positive TC-99m-PYP myocardial scans

Patients averaged 55.3 years in age (range 34 to 64 years) Six patients sustained inferior wall transmural MI (Q waves II III & aVF) and two anterior transmural MI (Q waves in Lead V1) Of the inferior MI patients one had ECG (No 1 in Table I and Fig 3) and TC-99m-PYP scan evidence of posterior wall involvement (R wave greater than S wave in Lead V1) and one (No 7) had involvement of the lateral wall (Q waves in Leads V5-6) All patients included had normal renal function documented by normal serum creatinine and a normal creatinine clearance in the first 24 hours after admission All remained in Killip Class I throughout hospitalization None of the patients required cardioversion or defibrillation and none had intramuscular injections No patient had any sustained hypotension during the course of the study All patients were discharged alive from the hospital.

During the study period (the first 50 hours after the onset of symptoms) six of eight patients

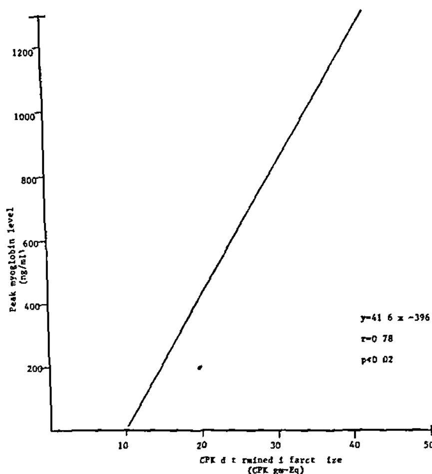


Fig 1 Correlation between peak myoglobin levels and CPK-determined infarction size

experienced two to five episodes (mean 3 5 per patient) of chest pain Of all the episodes of chest pain only one (patient No 1) had documentation of extension and that was posterior wall extension as noted by ECG

Myoglobin appearance and clearance characteristics (Table I)

All times were considered relative to the first onset of symptoms Normal serum myoglobin is less than 85 ng/ml The time of appearance of myoglobin relative to patient s first symptoms was 3 88 ± 0 64 hours In the four patients whose myoglobin was already elevated at the time of first blood sample the time from symptoms to first sample was arbitrarily considered appear ance time

The time from onset of symptoms to peak myoglobin levels was 6 88 ± 2 30 hours For all patients the average length of myoglobin eleva tion was 23 6 ± 7 41 hours

The serum half life of myoglobin calculated from the point of terminal descent from a loga rithm of myoglobin vs time display was 7.38 ± 2 80 hours

Comparison of CPK infarct size with peak myoglobin and myoglobin time index

Infarct size as determined by CPK correlated relatively well with the peak myoglobin level (r = 0 78 P is less than 0 02) (Fig 1) The correla tion between infarct size as determined by CPK and the area under the myoglobin concentration time plot was excellent and highly significant (r = 0 98 P is less than 0 001) (Fig 2)

It is also of note that an infarct as small as 7 6 CPK gm Eq is associated with an elevated serum myoglobin suggesting that an infarct at

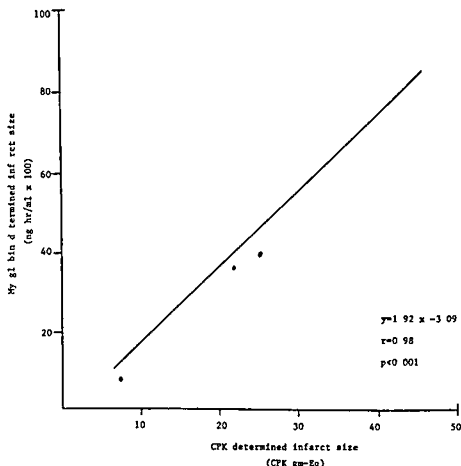


Fig 2 Correlation between myoglobin determined infarct size calculated from the area under the concentration time plot and CPK determined infarct size

least this small can be detected by an elevation in serum myoglobin

Discussion

Myoglobin is a small molecular weight heme protein for which a quick and sensitive radioimmunoassay is available Because of its rapid appearance there had been much enthusiasm for its use as a screening tool for acute myocardial infarctions However 50% of our patients with diagnostic ECG had normal initial myoglobin levels suggesting that despite its early appearance it may not be soon enough to warrant use as an emergency room screening tool This agrees with the findings of others[11] Myocardial and skeletal myoglobin cannot be differentiated and this lack of specificity also limits this use A recent review has discussed the causes of serum myoglobin elevation

The purpose of selection of patients with Killip Class I infarctions for inclusion in this report was to minimize alterations in renal blood flow Although these patients remained without evidence of altered hemodynamics or reduced perfusion the mechanism of cardiac myoglobin release and washout and the effects of changes in renal blood flow on myoglobin metabolism and clearance during myocardial infarctions are not known

The results of myoglobin kinetics here reported are similar to previous studies and confirm its rapid appearance and short half life after the onset of symptoms In uncomplicated infarctions the mean time to first elevation was about 4 hours and a peak level occurred at about 7 hours after the onset of symptoms The myoglobin remained elevated for an average of 24 hours with a mean half life being 7 4 hours

As pointed out in another study most previous work relates the appearance and clearance time to hospital admission rather than the onset of symptoms In one previous study when myoglobin were related to onset of symptoms peak levels were shown to occur 6 to 8 hours later We

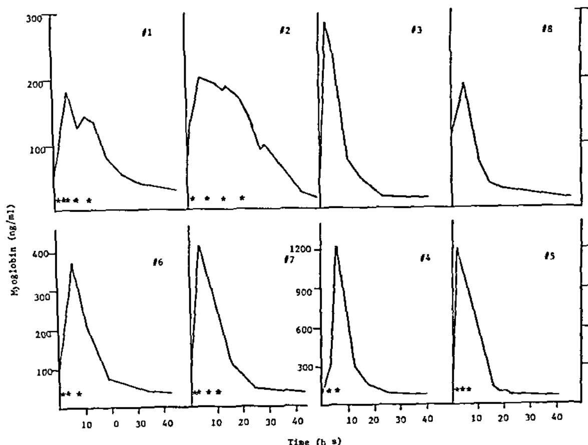


Fig 3 Serum myoglobin concentration time plot for each of the patients. Asterisks ( ) indicate time of onset of chest pain following admission

have also demonstrated that all infarcts in our group including one as small as 7 6 CPK gm Eq were associated with demonstrable increase at myoglobin levels This suggests that even small infarcts are associated with detectable myoglobin elevation if serum collection is properly timed

Comparison of infarct size as determined by standard CPK analysis with peak myoglobin levels seems to show some statistical significance Although in experimental animals peak levels have shown an extremely high correlation with histologic infarction size following coronary ligation this model of myocardial infarction may not completely resemble the clinical situation

There is a highly significant correlation between infarct size as determined by CPK and that determined from a myoglobin time index by simply calculating the area under the concentration time curve This suggests that myoglobin may be as good an indicator of infarction size as analysis of total CPK Whether its usefulness in these uncomplicated infarctions is valid and may be extended to complicated infarction deserves further study

As has been reported and demonstrated by several markers myocardial infarction is not an isolated event but may occur in separate episodes over hours or days [11] Myoglobin by its rapid appearance and clearance is capable of separating further episodes of myocardial necrosis as has been shown by Kagen and associates in the staccato phenomena of myoglobin release in myocardial infarctions Within the first 48 hours of an infarction conventional enzymes and evolutionary ECG changes prevent clear identification of post infarction chest pain as necrosis or reversible ischemia The single spike pattern of myoglobin (patients No 3 to 8) in Fig 3 probably indicates that the infarction occurred over a short period of time and further chest pain which did not produce further myoglobin elevation (patients No 4 to 7) within the four hour symptom to myoglobin release period did not indicate further necrosis However a plateau period (pa

tient No 2) or a second spike (patient No 1) suggests that the necrosis occurred over a longer period of time or occurred in several separate episodes

Conclusion

It has been shown[1-3] that myoglobin is one of the earliest appearing marker of myocardial infarction However our results demonstrate that a single determination of serum myoglobin obtained within the first few hours of the onset of clinical symptoms may not be a sensitive test for the early detection of myocardial necrosis and may be negative in up to 50% of transmural infarctions A level obtained at the time myoglobin was expected to peak (7 hours) might be more useful

It is reported[1] that in animal studies peak myoglobin levels correlated well with histologic infarction size In our study although correlation between CPK determined infarct size and peak levels exist the correlation between CPK determined infarct size and the myoglobin time index is much higher Our findings suggest that this may be a simple alternate method for estimating the size of uncomplicated myocardial infarctions Further studies are necessary before this data can be extrapolated to other clinical or hemodynamic subgroups of myocardial infarction

Pain occurring in the 48 hours following first onset of symptoms is a common problem in the coronary care unit Determining if this represents ongoing or repeated episodes of necrosis or reversible ischemia may be helpful in guiding therapy Sequential myoglobin determinations suggest that not all episodes of postinfarction pain represent necrosis but some represent ischemia Serial myoglobin levels because of their rapid appearance and clearance may be useful in following the progression or extension of an acute infarction

We wish to thank Dr Robert Roberts at Washington University for the CPK determination of the infar t size Ms Dorothy Plasziak and the nurses and staff of the Coronary Care Unit at Roger Williams Hospital for their assistance in the data collection and Ms Sandra Gavin for secretarial assistance in preparation of this manuscript

REFERENCES

1 Stone M J Willerson J T Gomez Sanchez C E and Waterman M R Radio immunoassay of myoglobin in human serum Results in patients with acute myocardial infarction J Clin Invest 56 1334 19 5
2 Donald T G Cloonan M J Neale C and Wilcken D E J Excretion of myoglobin in urine after acute myocardial infarction Br Heart J 39 29 19 7
3 Reichlin M Visco J P and Kloche F J Radioimmunoassay for human myoglobin Initial experience in patients with coronary heart disease Circulation 52 56 1978
4 Kagen L Scheidt S Roberts L Porter A, and Paul H Myoglobinemia following acute myocardial infarction Am J Med 58 177 1975
5 Saranchak H J and Bernstein S H A new diagnostic test for acute myocardial infarction J A M A 228 1251 1974
6 Willerson J T Buja L M Kulkarni P Parkey R W and Stone M J Factors which influence myoglobin release from cardiac cells and the localization of a pecific antibody to myoglobin in myocardial tissue (Abstr) Clin Res 25 4 8A 1977
7 Varki A Roby D Watts, H and Zatuchur J Serum myoglobin in acute myocardial infarction A clinical study and review of the literature AM HEART J 96 680 1978
8 Kuskelo I Kekki M and Wager O Kinetic behaviour of I labelled myoglobin in human beings, Clin Chim Acta 17 339 1967
9 Kagen L Scheidt S and Butt A Serum myoglobin in myocardial infarction The Staccato Phenomenon Am J Med 62 86 1977
10 Ahumada G Roberts R and Sobel B Evaluation of myocardial infarction with enzymatic indices Prog Cardiovasc Dis 28 405 19
11 Gilkeson G stone M Waterman M Ting R Gomez Sanchez C Hull A and Willerson J Detection of myoglobin by radioimmunoassay in human sera its usefulness and limitations as an emergency room screening test for acute myocardial infarction AM HEART J 95 70 19 8
12 Willerson J Poliner L Buja L Waterman W Gomez Sanchez C Templeton G and Stone M Myoglobinemia as a clue to the presence of acute myocardial infarction (Abstr) Clin Res 24 4 2A 1976
13 Rothkopt M Boerner J Stone M J et al Detection of myocardial infarction extension by CK B radioimmunoassay Circulation 59 268 1979
14 Reid P R Taylor D R Kelley D T et al Myocardial extension detected by precordial ST mapping N Engl J Med 290 123 1974
15 Mathey D Bleifeld W Bus H and Honrath P Creatine kinase release in acute myocardial infarction corr lation with clini al electrocardiographic and pathologic findings Br Heart J 37 1161 1975

Long-term results after aortic valve replacement with four different prostheses

Jon Dale, M.D.
Olaf Levang, M.D.
Ivar Enge, M.D.
Oslo, Norway

The ideal prosthetic heart valve should combine excellent durability, a wide opening, laminar blood flow, and minimal gradients; it should not traumatize blood cells or trigger thrombus formation. All these demands have so far not been fulfilled by any prostheses in spite of extensive research and development of new designs. In our hospital four types of aortic valve prostheses have been implanted during the seven year period from 1966 to 1973. First used was the Starr-Edwards ball valve type 1200 (SE 1200) with silicone rubber balls and metal cage, which was later replaced by type 2300 in which a Stellite hollow ball moved within a cloth covered cage.[1] The modifications were done primarily to avoid ball variation[2] and escape, but also to reduce the high incidence of arterial thromboembolic complications which had been reported to accompany the oldest type.

The need for anticoagulation in patients with prosthetis heart valves had early been recognized; it reduced the incidence of arterial thromboembolism, but only to some extent.[6] The incidence of thromboembolic episodes in our patients has previously been reported; it was found to be significantly lower with the newer modification of the ball valve, but it still represented a serious problem in spite of adequate anticoagulation, cerebral embolism being the most frequent manifestation.

Increased red cell breakdown was found to accompany implantation of the ball valves, and especially the SE type 2300 induced a considerable iron loss and in several patients frank hemolytic anemia.[8]

From 1971 disc valve prostheses have been used at this hospital. Two types were implanted, the Bjork-Shiley (BS) and Lillehei-Kaster (LK)[1] prostheses, both incorporating a free floating disc in an annular housing. The cage is slightly different in the two types; the LK prosthesis allows a wider opening and the disc closes against the ring, while the BS disc has minimal contact with the housing and allows a very slight regurgitation.

The incidence of thromboembolic complications was, however, not lower after disc valve implantation than in patients with the SE 2300 prosthesis, and thrombosis on the valve represented a particularly dangerous complication,[11] as confirmed by others.[1, 3] Red cell destruction was slight, especially in patients with the BS prosthesis, and hemolytic anemia did no longer represent a clinical problem.[1]

The present investigation was done in order to study the long term survival and clinical effect of valve replacement with the two types of Starr-Edwards ball valves and with the disc valve prostheses and to evaluate the influence of valve size on the clinical improvement.

Materials and methods

Altogether 449 patients received isolated aortic valves during a seven year period from 1967 and 1973. Until November 1968 valve type SE 1200 was implanted in 80 patients; thereafter the modified valve SE 2300 was used in 173 patients

From Medical D partment B, S   ic l Departm nt A, and the D partm nt for Rad logy, Rikshosp tal t, N tion l Hospital of Norway, Osl , Norway.

Recei ed f   publicat n J ne 1   19 9.
Accepted f   publi   tion Sept. 24, 19 9.

Reprint equests: D . J. D le, Medi l D partme t B, Rik hospital t, Osl 1, Norway.

000? 8/03/80/070155 + 08$00.80/0

Table I Comparison of preoperative characteristics of patients receiving the different valve types

	Patients with valve type			
	SE 1200	*SE 2300*	*LK*	*BS*
No of patients	80	1"3	9"	99
No of men	60	121	"6	6?
No of women	20	52	?1	3
No in functional Group IV	17	42	30	3?
No with arrhythmia	14	23	11	[illegible]
Mean age at operation (years)	1 3	52 6	53 3	54 6
Mean heart size (ml /M)	6 2	661	6 0	604

Table II Preoperative hemodynamic findings in patients in the four groups

	No of patients with valve			
	SE 1200	*SE 2300*	*LK*	*BS*
Aortic stenosis				
Gradient 100 mm Hg	16	25	13	19
Gradient 50 99 mm Hg	6	14	18	18
Aortic incompetence				
Severe	19	55	37	34
Less severe	10	14	9	5
Aortic stenosis and incompetence	29	65	20	23
Mitral stenosis	3	3	4	3
Mitral incompetence	7	20	6	14
Mitral stenosis and incompetence	8	10	1	2
Coronary heart disease	6	16	10	1?
Left ventricular aneurysm	1	2	2	3

From 1971 the BS and LK disc valves were inserted according to randomization in 196 individuals

Before operation a left side catheterization was always done in most patients by retrograde catheter introduction into the left ventricle and in some by transseptal catheterization Angiography included contrast injections into the ventricle and the aortic root and pressures were recorded Before 1970 selective coronary angiography was done in patients with angina later also in patients older than 50 years Thus coronary angiography was done in a larger proportion of the patients with disc than with ball valves

The operative technique and postoperative care remained largely unchanged during this period of time but some important changes were later introduced which have reduced the early mortality rate considerably This is the reason why patients operated later were not included in the study Oxygenation was achieved by a bubble oxygenator until 1970 thereafter a disc oxygenator with filters has been employed Light hypothermia 32 to 34° C was routinely used and the left coronary artery was always perfused The patients were heparinized with 300 I U of heparin per kilogram body weight and after operation the heparin activity was neutralized with protamine sulfate Oral anticoagulation was started after two to four days unless bleedings persisted

Follow up

The follow up examinations were performed at different times The first examination of the patients with ball valves was done in the autumn of 1972 when all except six met up Two years later the surviving patients were examined and only seven were unable to come

Similarly the follow up studies of the patients with disc valves were done early in 1975 and in the autumn of 1976 six patients did not report for the first and 23 did not report for the last examination

A questionnaire was sent to all patients physicians asking for additional information after each of the follow up examinations and relatives were contacted when necessary When patients had been admitted to other hospitals requests for reports were sent Thus the data presented were obtained from three different sources hospital records examination of the patients and information from doctors and relatives None of the patients were lost for follow up

At examination an exact history with emphasis on symptomatology and clinical course occurrence of arterial thromboembolic episodes or bleeding complications was obtained A careful

clinical examination was done including ECG x ray of heart and lungs and several blood tests regarding intravascular hemolysis and anemia platelet function and coagulation including control of anticoagulant therapy with the Thrombotest as previously reported[11, 13] Heart size was calculated in milliliters per square meter of body surface area[16, 1]

Criteria for the diagnosis of arterial thromboembolism have been described earlier[1, 5]

Results

The material is presented in Table I More women received BS than LK valves in spite of randomization The proportion of patients in functional Group IV according to the New York Heart Associations (NYHA) classification differed only insignificantly between the patient groups being slightly higher in the patients with disc valves Only minor differences appeared in the incidence of continuous arrhythmias mostly atrial fibrillation between the groups The mean age at operation rose slightly throughout the period mainly because some more individuals older than 70 years received disc valves than ball valves The mean preoperative heart volumes were 88 ml /M less in patients with BS than in those with the SE 1200 valve The differences were however not accompanied by similar deviations in the functional group distribution

The preoperative hemodynamic findings are listed in Table II No significant differences appeared in the distribution of severe stenosis with systolic peak gradients higher than 100 mm Hg or in severe aortic regurgitation with contrast reaching the apex of the left ventricle without being pumped out during the following systole or in the proportion of patients with combined stenosis and insufficiency Mitral incompetence not regarded serious enough to require mitral valve replacement was more frequent in the BS than the LK group of patients while mitral stenosis was most common in patients with ball valves Significant coronary artery stenosis or occlusion was found in approximately 10% of the patients

The type of operation performed is presented in Table III Mitral commissurotomy was more often done in patients with ball valves This reflects a gradual changes in policy regarding mitral valve operations with the preference of valve replacement for commissurotomy Aortocoronary bypass was introduced at the hospital in 1970 but was performed only in five patients who simultaneously received disc valves Resection of a left ventricular aneurysm was done in seven patients and in four previously implanted prostheses were replaced by disc valves

The mean time intervals from operation until the follow up examinations are presented in Table IV demonstrating that the patients with the oldest ball valve type were followed on an average more than six and a half years and the patients in the three other groups were followed approximately four and a half years

The long time survival calculated according to the actuarial method is illustrated in Fig 1 The early mortality rate (deaths within 30 days) remained fairly constant at 15% throughout the period and did not differ between patients with disc and ball valves The late mortality rate was remarkably similar in the four groups the recorded or actuarial five year survival rate being 65% in patients with ball valves and 68% in those with disc valve prostheses No significant differences

Table III Type of operations performed on the four patient groups

	Patient with valve type			
	SE 1200	*SE 2300*	*LK*	*BS*
Valve replacement alone	63	155	84	86
Valve + mitral commissurotomy	10	16	5	5
Valve + aortocoronary bypass			3	2
Valve + aneurysmectomy	1	1	2	3
Replacement of old valve			2	2
Emergency operations	6	11	8	9

Table IV Time from operation and to the first and second follow up studies in the four groups of patients

	Patients with valve type			
	SE 1200	*SE 2300*	*LK*	*BS*
Mean time to first examination (years)	4.7	2.7	2.5	2.5
Mean time to second examination (years)	6.7	4.7	4.3	4.3

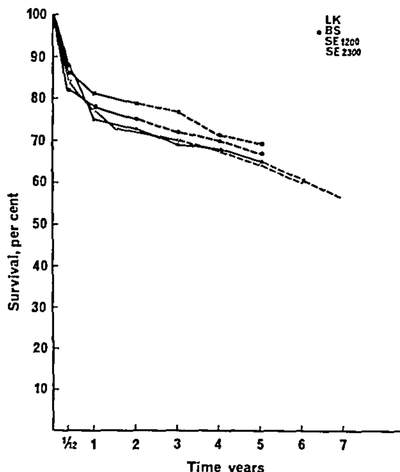


Fig 1 Long term survival after aortic valve replacement with the four different prostheses *The dotted lines indicate survival estimated by the actuarial method*

Table V Causes of late deaths after aortic valve replacement

	Patients with		
	Ball valve	*Disc valves*	*Total*
Myocardial failure	19	7	26
Arterial thromboembolism	6	3	9
Sudden death	6	3	9
Sepsis	5	1	6
Myocardial infarction	4		4
Intracranial bleeding	4		4
Mitral incompetence	1	2	3
Ventricular fibrillation	2	1	3
Reoperation	2		2
Rupture of aneurysm	1		1
Paravalvular leak	1		1
Cancer	2	2	4

appeared between any of the groups at any time

The most frequent causes of early death were in this order myocardial failure arrhythmia sepsis myocardial infarction and arterial thromboembolism Myocardial failure was responsible for an even higher proportion of late deaths and also frequent was sudden death as well as death from thromboembolic complications[6, 11] mostly cerebral emboli in ball valve patients and valve thrombosis in the others (Table V) Myocardial infarction and intracranial bleeding caused some deaths in patients with prosthetic ball valves

Table VI Mean heart size before and after aortic valve replacment

	Mean heart size (ml/M²)			
	SE 1200	*SE 2300*	*LK*	*BS*
Before operation	679	63	642	584
At first follow up	584	586	617	545
At second follow up	619	615	59	567

The heart size reduction from the preoperative examination until the first postoperative examination was most marked in patients with valve type SE 1200 who had the largest hearts before

Table VII Preoperative heart volumes in patients with isolated aortic valve disease who received smaller or larger valves

	Heart size (mL/M²)				
	Smaller valves		*Larger valves*		
	Mean	*SD*	*Mean*	*SD*	
SE 1200	545	143	719	168	$p < 0.01$
SE 2300	588	139	730	165	$p < 0.001$
LK	593	139	699	194	$p < 0.02$
BS	530	108	624	150	$p < 0.01$

operation but a significant reduction also occurred in the other groups (Table VI). From the first to the second follow-up, however, no further over-all improvement was found. The change in heart size in the individual patient may, however, not be due only to the type of valve implanted. Thus, an increase in heart size was frequently seen in patients with coexisting valvular or coronary heart disease. In order to evaluate the effect of valve type and size, patients with isolated aortic valve dysfunction were studied. The ball valve termed smaller were of size 10 A or less, corresponding to an inner diameter of 15.5 mm in type SE 1200 and to 14.3 mm in series SE 2300, while the orifice diameter was 18 mm or less in smaller disc valves of both types. The preoperative heart size of patients who had the smaller valves of the different types implanted was on an average approximately 100 ml less than in those with larger valves (Table VII). At operation, valve size had been selected according to the size of the aortic ostium. Implantation of the smaller ball valves of both series and especially type 2300 resulted in a very moderate reduction of heart size (Table VIII) and insertion of smaller disc valves also led to only a limited decrease in heart volumes. The disc valves did not represent an advantage over larger ball valves when reduction of heart enlargement is concerned. Indeed, the most marked reduction was obtained with the larger valves of the SE 1200 series, even if the orifice is considerably smaller than in the larger disc valves.

The mean functional group value was recorded according to the NYHA classification before and after valve replacement (Table IX). Most patients were in Functional Class 3. Individuals with disc valves were on an average in a slightly poorer clinical condition than the ball valve patients at the time of implantation. A consider

Table VIII Relation between the orifice diameter of the implanted valve and the reduction of heart size from before operation to the second follow-up examination

	Mean orifice diameter (mm.)	*Reduction of heart size (mL/M²)*			
		Smaller valves		*Larger valves*	
		Mean	*SD*	*Mean*	*SD*
SE 1200	16.4	45.0	74.8	162.5	1[illegible]6
SE 2300	14.7	37.4	149.5	119.3	211.5
LK	18.2	56.0	120.3	134.4	163.9
BS	18.4	57.9	70.2	108.0	138.4

Table IX Mean functional group according to NYHA Classification before and after operation of patients who survived the follow-up period

	Mean functional group			
	SE 1200	*SE 2300*	*BS*	*LK*
Before operation	3.18	3.18	3.31	3.36
At first examination	2.29	2.28	2.01	2.33
At second examination	2.34	2.31	2.29	2.42

Table X Preoperative functional group in patients with isolated aortic valve disease

	Functional group				
	Larger valves		*Smaller valves*		
	Mean	*S.D*	*Mean*	*SD*	
SE 1200	3.07	0.47	3.22	0.42	N.S
SE 2300	3.08	0.47	3.26	0.5	N.S
LK	3.29	0.51	3.12	0.53	N.S
BS	3.35	0.54	3.29	0.53	N.S

Table XI Relation between the orifice diameter of the implanted valves and clinical improvement expressed by NYHA group reduction

	NYHA group reduction				
	Smaller valves		*Larger valves*		
	Mean	*S.D*	*Mean*	*S.D*	
SE 1200	0.67	0.88	1.09	0.33	N.S
SE 2300	0.65	0.59	0.93	0.62	N.S
LK	1.13	0.54	1.11	0.80	N.S
BS	1.22	0.80	1.13	0.68	N.S

able functional improvement occurred in all groups especially in patients with BS valves until the first follow up examination The improvement seemed however to reach a maximum after a few years whereafter the condition remained constant or deteriorated slightly

The preoperative functional impairment did not differ significantly between patients who received smaller or larger valves (Table X) The effect of valve size was evaluated in patients without other valvular defects or CHD (Table XI) Significant differences in the improvement which occurred in all eight groups did not appear although a slightly less marked positive development was recorded in patients with the smaller ball valves than with other types

Discussion

The early mortality rate after aortic valve replacement was similar in patients with the different valves indicating that prosthesis design was of little importance The early death rate was comparable with or higher than that found by others and the most common causes of death were largely the same The majority of early deaths were due to complications unrelated to the prosthesis such as myocardial failure and arrhythmia indicating that the preoperative condition of the myocardium is of great importance for early survival The early mortality rate has later been reduced considerably in our hospital chiefly because of improved techniques such as the introduction of extreme hemodilution during extracorporeal circulation local cooling without cannulation of the coronary arteries and better prophylaxis against ventricular arrhythmias

Surprisingly even the late mortality rate appeared to be independent of valve type Deaths caused by thrombus formation on the prosthetic valve such as cerebral embolism valve dysfunction and sometimes myocardial infarction might to some extent be related to valve type and function One would anticipate that the lesser orifice and higher peak systolic gradients across the ball valves especially the 2300 prosthesis would represent an extra load on the left ventricle and thereby carry a slightly worse prognosis than the disc valves Again the importance of an adequate myocardial function for long term survival is evident as also reported by others An exact estimation of the mortality rate after aortic disc valve implantation can not be made since only nineteen late deaths occurred during the observation period which was shorter than in the groups of patients with ball valves where fifty three late deaths were recorded Although a larger material could have provided a better basis for a comparison of late death rates our results allow the conclusion that the introduction of disc valves has not considerably reduced the late mortality rate after aortic valve replacement The importance of myocardial function indicates that late survival can be better increased by earlier operations than by improved design Valve related causes of death such as arterial embolism or valve thrombosis might be reduced with combined antithrombotic therapy where drugs affecting platelet function such as acetylsalicylic acid or dipyridamole are added to anticoagulants

The moderate effect of aortic valve replacement on heart size is in accordance with the findings of others The maximum reduction appears to be obtained rather early after operation while no marked improvement can later be achieved regardless of valve type Thus the preoperative heart size is the main determinant also for the postoperative size which again stresses the importance of myocardial function for the late results The most marked reduction was found in patients with isolated aortic valvular lesions indicating that additional heart disease may negatively influence size and coexisting valvular coronary or other heart disease was the cause of the slight average increase in heart volumes from the first to the second examination

The less favorable development of heart size in patients who received smaller valves instead of larger ones reflects the importance of a wide orifice in the implanted valve although part of the reduction observed can be explained by the preoperative heart enlargement The minimal improvement in patients with smaller ball valves of series 2300 is in accordance with the high systolic gradients found across these valves Surprisingly the larger disc valves did not appear to be superior to the ball valves even with regard to heart size reduction as would have been expected from the higher gradients across the ball valves in type 2300 in particular Peak and mean systolic gradients are low across aortic disc valves especially the BS prothesis and the heart volume reduction therefore does not fully

reflect the hemodynamic advantage of the BS prosthesis Possibly the slight leakage in diastole through the disc valves particularly the BS prosthesis might have some influence It appears however than an enlarged heart can be reduced only to a certain extent and that the condition of the myocardium is the limiting factor which determines the improvement that can be obtained even with the best prosthesis

Similar considerations can be made regarding the clinical improvement that occurred The patients with disc valves were on an average in a slightly poorer condition than those with ball valves as judged from the NYHA group classification Functional class assessment is however subjective and the criteria are not equally easy to apply to all symptoms the patients experienced before operation most frequently dyspnea and angina on exertion fatigue and syncope After valve replacement syncope no longer occurred angina or dyspnea had disappeared or was less easily precipitated while fatigue and dizziness were the most common complaints These symptoms may be due to anesthesia or altered blood flow during operation especially the effect of extracorporeal circulation Continued microembolization may contribute or the symptoms may be unmasked by the disappearance of others

The clinical improvement was considerable and corresponded to a reduction of one functional class in most patients slightly less in those with ball than in those with disc prostheses The clinical effect appeared to be greater than could be expected from the heart size reduction

The considerable initial improvement did however not continue and a quite stable clinical condition was reached in most patients while a slight deterioration was noted in several others Even if a less favorable development often could be attributed to coexisting heart disease the results indicate certain long term limitations to the effect of aortic valve replacement The less pronounced clinical improvement in individuals with smaller ball valves especially of type 2300 is in accordance with the minimal heart size reduction found and could be anticipated from the high systolic gradients across such valves The equally satisfactory effect on functional capacity of larger and smaller disc valves and of larger ball valves indicates that the clinical course is less influenced by valve modifications than by myocardial function

Although more sensitive criteria might reveal a clinical advantage of the hemodynamically better BS valves our results suggest that more can be gained by earlier valve replacement than by further refinement of valve design

Summary

The long term results after implantation of isolated aortic ball and disc prostheses were studied The Starr Edwards ball valve type 1200 was first used in 80 patients thereafter type 2300 was used in 173 later the Bjork Shiley and the Lillehei Kaster disc valves were implanted in 99 and 97 patients according to randomization The surviving patients with the oldest ball valve were examined after 4 7 and 6 7 years on an average the others after approximately 2 5 and 4 5 years

The early mortality rate was 15% and did not differ between the four groups Even the late mortality rate was quite similar in the patient groups the five year survival rate being 65% in patients with ball valves and 68% in those with disc valves as estimated with the actuarial method

The average reduction of heart size was moderate and quite similar in the four groups most pronounced in patients with isolated aortic valve involvement The reduction was greater in patients who received larger rather than smaller valves of all types

Aortic valve replacement resulted in a considerable clinical improvement in patients with all valve types it corresponded largely to one functional group according to the NYHA classification The heart size reduction and functional improvement was most moderate in patients with smaller ball valves which could be anticipated from higher peak systolic gradients than across the other valves used No significant differences appeared between patients with the larger valves of the four types

The initial improvement as recorded either by reduction of heart size or increase in functional capacity had reached its maximum at the first follow up examination in most patients

The preoperative myocardial function appeared to be the limiting factor which determined what late results could be obtained regardless of the type of valve implanted The results therefore indicate that more can be achieved by earlier valve replacement than by improving the prostheses

REFERENCES

1. Herr R H Starr A Lfene W R Wood J A, and Bigelow J C Aortic valve replacement A review of six years experience with the ball valve prosthesis Ann Thorac Surg 3 1?0 1?68
2. Chin H P, Harrison E C Blankenhorn D H and Moscanin J Lipids in silicone rubber valve pro theses after human implantation Circulation 43 and 44(Suppl I) ?? 1? I
3. Fleming J Hamer J, Hayward G, Tubbs O S and Hill I Long term results of aortic valve replacement with the Starr Edwards valve Br Med J 1 139 19?1
4. Friedli B Aerichide N Grondin I and Campeau L Thromboembolic complications of heart valve prostheses Am Heart J 81 ?02 1??1
5. Matloff J M Collins J J, Sullivan J M Corlin R, and Harken D Control of thromboembolism from prosthetic heart valves Ann Thorac Surg 8 133 1969
6. Dale J Arterial thromboembolic complications in patients with Starr Edwards aortic ball valve prostheses Am Heart J 91 6?3 197?
7. Barnhorst D A, Oxman H A Connolly D C Pluth J R, Danielson G K, Wallace R B and McGoon D C Long term follow up of isolated replacement of the aortic or mitral valve with the Starr Edwards prosthesis Am J Cardiol 35 228 19?
8. Myhre E, Dale J and Rasmussen K Erythrocyte destruction in different types of Starr Edwards aortic ball valves, Circulation 42 1? 1? 0
9. Bjork V O, Olin C, and Rodriguez L Comparative results of aortic valve replacement with different prosthetic heart valves J Cardiovasc Surg 13 ?68 1??2
10. Kaster R L Lillehei C W and Starek, I J K The Lillehei Kaster pivoting disc aortic prosthesis and a comparative study of it pulsatile flow characteristics with four other prostheses Am Soc Artif Intern Organs 16 233 19?0
11. Dale J Arterial thromboembolic complications in patients with Bjork Shiley and Lillehei Kaster aortic disc valve prostheses Am Heart J 94 101 19?7
12. Ben Zvi, J Hildner F J Chandraratna I A, and Samet I Thrombosis on Bjork Shiley aortic valve prosthesis Am J Cardiol 34 ?38 19?4
13. Forman R Beck W and Barnard C N Results of valve replacement with the Lillehei Kaster disc prosthesis Am Heart J 94 ?2, 19?8
14. Dale J and Myhre E Intravascular hemolysis in the late course of aortic valve replacement Relation to valve type size and function Am Heart J 96 24 19?8
15. Dale J Myhre E Storstein O Stormorken H and Efskind L Prevention of arterial thromboembolism with acetylsalicylic acid A controlled study in patients with aortic ball valves Am Heart J 94 101 19?
16. Jonsell S A method for determination of the heart size by teleroentgenography (A heart volume index) Acta Radiol 20 ? 19?
17. Amundsen I The diagnostic value of conventional radiological examination of the heart in adults Boston Oslo London 1? J O ?? University Press
18. New York Heart Association Nomenclature and criteria for diagnosis of the heart and blood vessels ed New York 19?3
19. Rubin J W Moore H V Hillson R F and Ellison P G Thirteen years experience with aortic valve replacement Am J Cardiol 40 3?? 19??
20. Pellegrini A, Marcazzan E Peronace B de Gasperi D Gordini F and Mombelloni G Ten years experience in heart valve replacement with artificial prostheses Immediate and long term results in 1 ?1? cases J Cardiovasc Surg 16 ?12, 19??
21. Rossiter S J Hultgren H N Kosek, J C Wuerflein R D and Angell W W Ischemic myocardial injury with aortic valve replacement and coronary bypass Arch Surg 109 6?2, 19?4
22. Ison O W, Williams C D, Falk E A Glassman E, and Spencer F C Long term evaluation of cloth covered metallic ball prostheses J Thorac Cardiovasc Surg 64 3?4 19?2
23. Storstein O and Efskind L Immediate and late results of aortic valve replacement Scand J Thorac Cardiovasc Surg 6 1?4 19??
24. Kloster F E, Herr R H, Starr A and Griswold H E Hemodynamic evaluation of a cloth-covered Starr Edwards valve prosthesis Circulation 39 and 40(Suppl I) 119 19??
25. Reis R L Clancy D L O Brien K Epstein S E and Morrow A G Clinical and hemodynamic assessment of fabric-covered Starr Edwards prosthetic valves, J Thorac Cardiovasc Surg 59 8? 1??0
26. Bryant L R Trinkle J K Spencer F C Danielson G K Shabetai R, and Reeves J T Cardiac valve replacement Results in patients with advanced disability JAMA 216 996, 1? 1
27. Sullivan J M, Harken D E and Gorlin R Pharmacologic control of thromboembolic complication of cardiac valve replacement N Engl J Med 284 1391 19?1
28. Nitter Hauge S Hall K V Froysaker T and Efskind L Aortic valve replacement One year result with Lillehei Kaster and Bjork Shiley disc prostheses Am Heart J 88 23 19?4
29. Bjork V O Holmgren A, Olin C and Ovenfors C O Clinical and hemodynamic results of aortic valve replacement with the Bjork Shiley tilting disc valve prosthesis Scand J Thorac Cardiovasc Surg 5 1? 19?1
30. Levang O Nitter Hauge S, Levorstad K and Froysaker T Aortic valve replacement A comparative study between Lillehei Kaster and Bjork Shiley disc valve prosthesis Central hemodynamic and its relation to clinical results and left ventricular function Scand J Thorac Cardiovasc Surg (In press)

Crossed atrioventricular connections

Fause Attie, M.D.
Luis Muñoz Castellanos, M.D.
Jacobo Ovseyevitz, M.D.
Ismael Flores Delgado, M.D.
Mario R. Testelli, M.D.
Alfonso Buendia, M.D.
Jorge Kuri, M.D.
Bernardo Molina, M.D.*
Mexico City, Mexico

Some papers have been published recently about complex congenital heart diseases in which the cardiac connections are not associated with concordant or discordant atrioventricular relations. We named this type of malformation crossed atrioventricular connections (criss-cross heart) which may be accompanied by different types of ventriculo-arterial connections. Crossed atrioventricular connections have an anomalous position of the interventricular septum and the ventricles lose their usual position partially or totally and may become superior and inferior.

We have studied four cases of crossed atrioventricular connections, three concordant and one discordant. The visceral situs, the atrioventricular connections, the spatial position of the ventricles, and the characteristics of the ventriculo-arterial connections were analyzed.

We have reviewed the cases reported so far in the literature and propose a classification for this anomaly.

Case reports

Case No. 1. A 13-year-old male patient was admitted in the hospital to diagnosis. There was a history of cyanosis since birth and moderate physical intolerance. A systolic-diastolic cardiac murmur was heard along the left sternal border. The electrocardiogram revealed sinus rhythm, left axis deviation, and biventricular hypertrophy. The chest roentgenogram showed an enlarged heart and increased pulmonary blood flow. The aorta formed the left superior border of the heart (Fig. 1). Cardiac catheterization revealed systemic pressures in both ventricles with identical pressures in the pulmonary artery. There was a significant right to left shunt.



Fig. 1. Frontal view of plain chest x-ray. Observe the aorta (*Ao*) forming the left superior border of the heart. *L* = liver; *S* = stomach.

Selective angiocardiograms were performed in the four cavities. The right atrial injection showed the right atrium to be in continuity with

From the Departments of Pediatric Cardiology and Embryology, Instituto Nacional de Cardiología Ignacio Chávez, Mexico.

Received for publication July 16, 1979.
Accepted for publication Aug. 1979.

Reprint requests: Fause Attie, M.D., Head, Pediatric Cardiology, Instituto Nacional de Cardiología, Juan Badiano 1, Mexico 22, D.F., Mexico.
*B n t t n

0002-8703/80/020163 + 10$01.00/0 © 1980 The C. V. Mosby Co.

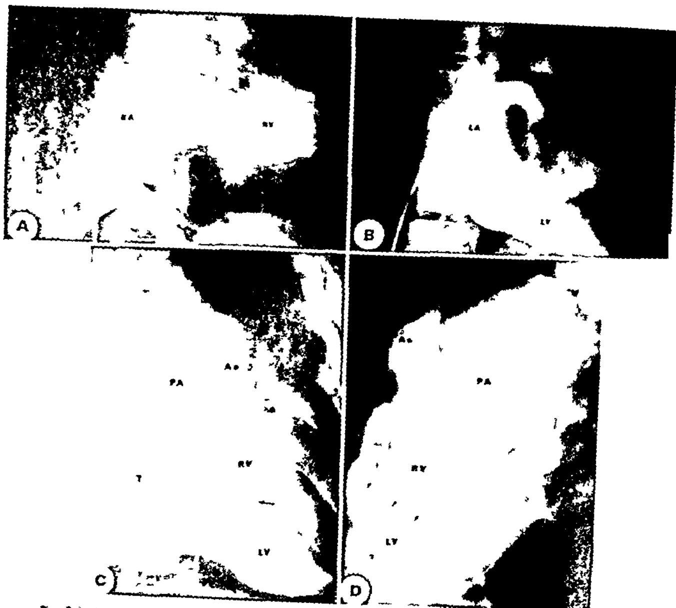


Fig 2 A through D Angiocardiogram from a patient with situs solitus concordant crossed atrioventricular connection and double-outlet right ventricle A View showing right atrium (RA) with opacification of the morphological right ventricle (RV) placed on the left and above B Injection into the left atrium (LA) showing the morphological left ventricle (LV) placed below C Frontal view of right ventriculogram Both great arteries are seen with the aorta (Ao) to the left of the enlarged pulmonary artery (PA) The morphological left ventricle was opacified by way of an ill-defined ventricular septal defect The interventricular septum was horizontally oriented (arrows) D Selective left ventriculogram in lateral projection The right ventricle and both great arteries were opacified by way of the ventricular septal defect Note the abnormal position of the septum that is outlined

the inflow portion of the right ventricle situated on the left and above (Fig 2A) The left atrium was connected to the left ventricle lying below (Fig 2B) The two ventricles were separated by an interventricular septum positioned in the horizontal plane Both great arteries arose from the right ventricle with the aorta anterior and to the left of the pulmonary artery (Fig 2C and D)

Case No 2 A 4 month old male patient was admitted with cyanotic congenital heart disease Physical examination revealed a Grade 3/6 systolic murmur over the precordial area There was moderate hepatomegaly The chest x ray film showed an enlarged heart and markedly increased pulmonary vascularity The electrocardiogram suggested biventricular hypertrophy Cardiac

Fig 3 A through C Angiocardiogram from a case with situs solitus discordant atrioventricular connections, and normally related and connected great arteries. *A* View of right atrium (*RA*) showing discordant atrioventricular connections *B* Ventriculogram depicting left ventricle (*LV*) From this injection the hypoplastic right ventricle (*rv*) and both arteries were opacified *C* Lateral view of left ventriculogram The aorta (*Ao*) is arising from this ventricle The small right ventricle is opacified via a ventricular septal defect (*arrow*)

catheterization was carried out Systemic pressures were recorded in both ventricles and great arteries

Biplane angiocardiograms were performed in both the right atrium and left ventricle The right atrium was connected to the left ventricle (Fig 3*A*) Both great arteries opacified simultaneously The main pulmonary artery was oriented from right to left (Fig 3*B*) In the lateral projection the left ventricle was posterior and inferior The great arteries were normally connected and related (Fig 3*C*) The postmortem study revealed situs solitus with juxtaposition of both atrial appendages The morphological right atrium drained to a morphological left ventricle situated on the left



Fig 4 Frontal view of thoracic roentgenogram The aorta (*Ao*) is forming the right superior margin of the heart *L* = liver *S* = stomach.

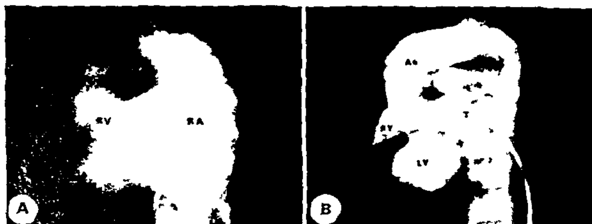


Fig 5.A and B Angiocardiogram from a patient with situs inversus, concordant crossed atrioventricular connections, and transposition of the great arteries A Injection into the right atrium (RA) with opacification of the morphological right ventricle (RV) well visualized in B B Right ventriculogram The catheter passed through the tricuspid valve (T) The right ventricle is small and the aorta (Ao) is arising from it The morphological left ventricle (LV) placed below was opacified via a ventricular septal defect

Fig 5 C through E Angiocardiogram from same patient as in Fig 4 and B C Left atriogram showing the connection of the LA with the morphological left ventricle D The left ventricle (LV) is well visualized and connected to the pulmonary artery (PA) Notice in B and D the anomalous position of the interventricular septum E Lateral projection shows the abnormal position of the tricuspid valve (T) anterior and superior



Fig 6 A through C *A* Right ventriculogram revealing the morphological right ventricle above and displaced to the right The tricuspid ring has an abnormal position *B* and *C* Frontal and lateral projections showing the inferior and posterior left ventricle (*LV*) Observe in *C* the abnormal relation between the posteroinferior mitral valve and anterosuperior tricuspid valve (Compare with Fig 5E)

and below The left atrium was connected to a hypoplastic right ventricle placed on the right and above There was a membranous type ventricular septal defect The arteries were normally related and connected with the pulmonary artery oriented from right to left

Case No 3 A six year old boy had experienced cyanosis and cyanotic spells from the first year of life Physical examination revealed the liver on the left and the cardiac apex to the right There was a Grade 4/6 systolic ejection murmur in the second right intercostal space The second heart sound was very loud in the same area

The electrocardiogram suggested a situs inversus and right ventricular hypertrophy Chest x ray confirmed the presence of situs inversus and dextrocardia normal cardiac size and a prominent right superior border formed by the aorta (Fig 4) Cardiac catheterization showed systemic pressure in both ventricles and the aorta

Selective angiocardiograms were performed in both atria and in the right ventricle The visceral situs inversus was noticeable (Figs 5A and C) The right atrium was connected to the right ventricle placed above (Figs 5A and B) the morphological left atrium was connected to the left ventricle located inferiorly (Figs 5C and D) The interventricular septum was horizontally oriented There was transposition of the great arteries with an anterior and right sided aorta

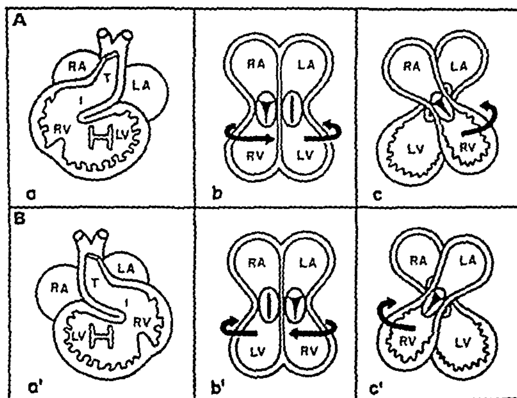


Fig 7 Diagrams of morphogenesis of crossed atrioventricular connections. Above, a D-loop *(a)* establishes concordant atrioventricular connections *(b)* before the abnormal rotation of both ventricles *(c)*. Below, an L-loop *(a')* which originates discordant atrioventricular connections *(b')* before the abnormal rotation of the ventricles *(c')*. *RA* = morphological right atrium; *LA* = morphological left atrium; *RV* = morphological right ventricle; *LV* = morphological left ventricle; *I* = infundibulum; *T* = truncus.

Infundibular pulmonic stenosis and a ventricular septal defect were noticeable (Fig 5D). The tricuspid ring was anterior and superior (Fig 5E).

This patient underwent palliative surgery with a Blalock-Taussig anastomosis.

Case No 4 In a seven year old boy, moderate physical intolerance and late cyanosis were noted since he was 4 years of age. The liver was found on the left and the cardiac apex to the right. A continuous murmur was heard in the second right intercostal space and a systolic ejection murmur was heard in the third right interspace.

The electrocardiogram showed situs inversus and biventricular hypertrophy. The chest x ray films confirmed the situs, revealed discrete cardiomegaly and decreased pulmonary blood flow. Cardiac catheterization proved the same pressures in both ventricles and the aorta. The systolic pressure in the pulmonary artery was normal.

Biplane angiocardiograms were performed in both ventricles. The catheter was passed from a left sided right atrium into an anterior and superior right sided right ventricle (Fig 6A). The morphological left ventricle had an inferior position (Fig 6B and C). The tricuspid and mitral valves had an almost anteroposterior relationship with the former slightly displaced to the right and above. The interventricular septum had an oblique direction. Both great arteries arose from the right ventricle with an anterior and left sided aorta.

Discussion

Crossed atrioventricular connections are congenital heart malformations in which the spatial position of the ventricles is not in accordance with the position of the atria to which they are connected.

The connection would depend on a previous atrioventricular relation given by the type of bulboventricular loop. A concordant loop for a given type of visceral situs would end in a concordant connection, while a discordant bulboventricular loop would end in a discordant connection.

In crossed atrioventricular connections an

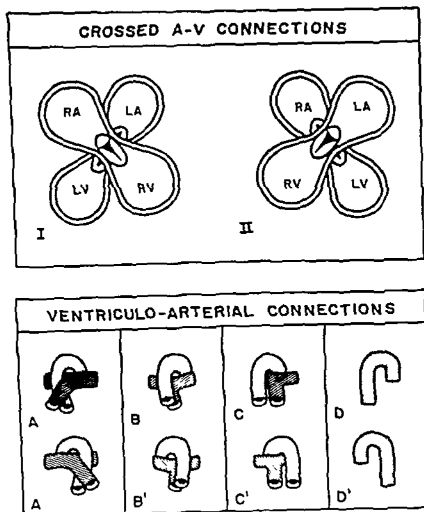


Fig 8 The diagrams I and II show concordant and discordant crossed atrioventricular connections respectively. Each one may be accompanied by all of the types of ventriculo arterial connections shown below. A A Normally related great arteries. B B Anterior aorta (transposed or malposed). C C Side by side great arteries (transposed or malposed). D D' Persistent truncus arteriosus. *RA* = morphological right atrium. *RV* = morphological right ventricle. *LA* = morphological left atrium. *LV* = morphological left ventricle.

abnormal rotation of both ventricles would occur after those connections were established moving both ventricles and their atrioventricular valves to the opposite side from their original position, i.e., in a case of situs solitus with concordant atrioventricular connections the morphologic right ventricle would rotate to the left with its atrioventricular valve while the left ventricle would move to the right also with its atrioventricular valve (Fig 7A). In situs solitus with discordant connections the right atrium is connected with the right sided left ventricle and the left atrium is connected with a left sided right ventricle; afterwards the right ventricle rotates toward the right with its atrioventricular valve and the left ventricle would turn to the left also with its atrioventricular valve. The tricuspid valve crosses in front of the mitral valve as it does in cases with concordant connections (Fig 7B). For situs inversus we would have the mirror image of the process observed in situs solitus either with concordant or discordant connections.

The horizontal position of the interventricular septum can be explained by a lack of descent of the right ventricle previous to its ventro medial rotation.

Up to this time there are 36 cases reported in the literature[1] of which 35 were in situs solitus and one with visceral heterotaxia.

From our own material two cases were in situs inversus both with concordant atrioventricular connections. From the 40 reported cases including ours 27 had concordant connec

Table I Crossed atrioventricular connection

Atrioventricular connection	Ventriculo-arterial connections
A Concordant	Normally connected great arteries Anterior aorta (trans or malposed) Side by side great arteries (trans or malposed)
B Discordant	Double-outlet right ventricle Double-outlet left ventricle Single outlet

Situs solitus or inversus.

tions ' and 13 were discordant ...

There are different types of ventriculo arterial connections ' such as in other congenital heart malformations The most common is transposition of the great arteries in its various forms less frequently double outlet right ventricle pulmonary atresia * normally related great arteries as Case 2 of Sieg and associates and the second of our own series and finally side by side great arteries [1]

There has not been described any case with persistent truncus arteriosus (Figs 8 I and II D and D) We may expect cases with isolated crossed atrioventricular connections (Figs 8 IA and IIA) in which the spatial position of normally related great arteries does not correspond to the spatial position of the ventricles as in isolated ventricular inversion described by Van Praagh and Van Praagh

If we consider the visceral situs and the atrioventricular connections we may classify these cardiac malformations into two separate groups one concordant and one discordant and we can expect that each one may be associated with different types of ventriculo arterial connections either with single or double outlet ventricle (Table I)

Criss-cross hearts are with rare exception complex congenital heart malformations and for this reason they are difficult to diagnose The type of atrioventricular or ventriculo arterial connections and the presence or absence as well as the degree or size of pulmonary stenosis or septal defects will be responsible for the clinical and hemodynamic pictures Most of the published cases show transposition of the great arteries associated with septal defect and pulmonary stenosis so we can find early cyanosis and symptomatology very common in those congenital heart malformations with decreased pulmonary blood flow

The x ray films are not of great value We have observed the aorta on the left in situs solitus or on the right in situs inversus These findings suggest that the great arteries are not in their usual place The abnormal situation of the aorta suggests a complex anomaly This condition with crossed atrioventricular connection should be included in the differential diagnosis along with corrected transposition of the great arteries some forms of double outlet right ventricle and malposition of the great arteries [1]

Atrioventricular connections were determined in three cases by means of the right and left atriograms In the first two the morphological right ventricle was situated on the opposite side while the left ventricle was located below In the third case discordant connections were established when the left ventricle was opacified in the opposite side and below

In the fourth case it was observed that the tricuspid and mitral valves had an almost anteroposterior relationship with a moderate displacement of the former to the right an unusual position for this type of visceral situs When we compare the position of the ventricular cavities with the other case in situs inversus we observe the existence of various degrees of ventricular rotation In this case the interventricular septum had an intermediate position because of a partial rotation of the ventricles This finding supports the existence of an abnormal rotation after septation

Due to the morphologic features of this cardiac anomaly the systematic diagnosis of congenital heart malformations has been reviewed It nomenclature was based primarily on relations and more recently on connections [1] In situs solitus a D loop indicated that the right ventricle was on the right and an L-loop situated the right ventricle on the left After the reports of criss cross hearts we may conclude that this type of bulboventricular loop produces atrioventricular connections regardless of the final spatial position of the ventricles

The importance of the type of loop is seen when we consider that most of the cases with criss cross hearts show concordant connections just as in other cardiac malformations without "criss cross" type of atrioventricular connections

When we consider the rules for localizing the ventricles by means of the position of the great arteries,[1] these become difficult to apply when the ventricles are not in their usual right and left position. For this circumstance, the presence of either a right- or a left-sided aorta makes the localization of its corresponding ventricle(s) difficult. These rare but distinctive anatomic relationships with crossed atrioventricular connections with unusual spatial orientation of the ventricles are of theoretic importance because they are exceptions to the rules for systematic diagnosis of congenital cardiovascular anomalies.[1] Moreover, they are of clinical significance when surgical repair is considered.

Summary

Four cases of crossed atrioventricular connections are described. All of them were diagnosed at cardiac catheterization by angiocardiography and one was examined pathologically. Two possessed situs solitus, one with concordant connections and the other with discordant connections; the other had two situs inversus, both of them with concordant connections. Two had double outlet right ventricle; one had transposition of the great arteries and the other had normally related and connected great arteries. These cases have been interpreted as representing abnormal rotation of the ventricles following sepatation. A review of 36 cases previously reported on and our own cases suggests that most patients have concordant atrioventricular connections. There are many types of ventriculo-arterial connections, the most frequent being transposition of the great arteries. There has not been any case reported with persistent truncus arteriosus. On the basis of atrioventriculo-arterial connections, we propose a classification for this malformation. We discuss the importance of the bulboventricular loop in the type of atrioventricular connections, some clinical implications for the diagnosis, and analyze the value of the rules to localize the ventricles by means of the position of the great arteries.

We gratefully acknowledge the secretarial assistance of Miss Laura Illescas.

REFERENCES

1. Shinebourne E A, Macartney F J, and Anderson R H: Sequential chamber localization—the logical approach to diagnosis in congenital heart disease. Br Heart J 38:327, 1976.
2. Anderson R H: Another look at cardiac embryology. *In* Yu P N, and Goodwin J F, editors: Progress in Cardiology, ed 7. Philadelphia, 1978, Lea & Febiger, p 1.
3. Anderson R H, Shinebourne E A, and Gerlis L M: Criss-cross atrioventricular relationships producing paradoxical atrioventricular concordance or discordance. Circulation 50:176, 1974.
4. Ando M, Takao A, Nihmura I, and Mori K: Crossing atrioventricular valves. A clinical study of 8 cases (Abstract). Circulation 54 (Suppl. II):90, 1976.
5. Anderson K R, Lie J T, Sieg K, Hegler D J, Ritter D G, and Davis G D: A criss-cross heart. Detailed anatomic description and discussion of morphogenesis. Mayo Clin Proc 52:569, 1977.
6. Sieg K, Hegler D J, Ritter D G, McGoon D C, Maloney J D, Seward J B, and Davis G D: Straddling right atrioventricular valve in criss-cross atrioventricular relationship. Mayo Clin Proc 52:561, 1977.
7. Symons J C, Shinebourne E A, Joseph M C, Lincoln C, Ho Y, and Anderson R H: Criss-cross heart with congenitally corrected transposition: report of a case with d-transposed aorta and ventricular preexcitation. European J Cardiol. 5/6:493, 1977.
8. Sato K, Ohara S, Tsukaguchi, I, Yasui, K, Nakada T, Tamai M, Kobayashi Y, and Kosuka T: A criss-cross heart with concordant atrioventriculo-arterial connections. Circulation 57:396, 1978.
9. Freedom R M, Culham G, and Rowe R D: The criss-cross and superoinferior ventricular heart. An angiocardiographic study. Am J Cardiol 42:620, 1978.
10. Kinsley R H, McGoon D C, and Danielson, G K: Corrected transposition of the great arteries. Associated ventricular rotation. Circulation 49:574, 1974.
11. Guthaner D, Higgins, C B, Silverman J F, Hayden W G, and Wexler L: An unusual form of the transposition complex. Uncorrected levo transposition with horizontal ventricular septum. Report of two cases. Circulation 53:190, 1976.
12. Waldhausen J A, Pierce W S, and Whitman W: Horizontal interventricular septum in congenital heart disease. Surgical considerations. Ann Thorac Surg 23:271, 1977.
13. De Vries, P A, and Saunders, J B de C M: A Development of the ventricles and spiral outflow tract in the human heart. A contribution to the development of the human heart from age group IX to age Group XV. Contrib Embryol. 258:87, 1962.
14. Kramer T Y: The partitioning of the truncus and conus and the formations of the membranous portion of the interventricular septum in the human heart. Am J Anat 71:343, 1942.
15. Kjellberg S R, Mannheimer E, Ruddhe U, and Jonsson B: Diagnosis of Congenital Heart Disease. Chicago, 1959, Year Book Medical Publishers, Inc., p 811.
16. Lev M, and Rowlatt U F: The pathologic anatomy of mixed levocardia. A review of thirteen cases of atrial or ventricular inversion with or without corrected transposition. Am J Cardiol. 9:216, 1961.
17. Wagner H R, Alday L F, and Vlad P: Juxtaposition of the atrial appendages. A report of six necropsied cases. Circulation 42:157, 1970.
18. Van Praagh R: Segmental approach to diagnosis in congenital heart disease. *In* Bergsma D, editor: Birth defects, vol VIII. Baltimore, 1972, the Williams & Wilkins Company, p 4.
19. Franco Vazquez, J S, Perez Trevino G, and Gaxiola A: Corrected transposition of the great arteries with

extreme counter clockwise torsion of the heart Acta Cardiol (Bruxelles) 28 636 1973
20 Van Praagh R and Van Praagh S Isolated ventricular inversion A consideration of the morphogenesis definition and diagnosis of nontransposed and transposed great arteries, Am J Cardiol 17 395 1966
21 Van Praagh R Pérez Trevino C Reynolds J L Moes C A F Keith J D Roy D L Bellcourt O Weinberg P M and Parisi L F Double outlet right ventricle (S D L) with subaortic ventricular septal defect and pulmonary stenosis Am J Cardiol 35 42 1975
22 Tarra Bossa I G Attie F Munoz L Kuri Alfaro J Zamora C and Buendia A Doble cámara de salida de ventrículo derecho con aorta anterior e izquierda Arch Inst Cardiol Mex 48 573 1978
23 Attie F and Mispireta J Discordancias auriculoventriculares Mexico 1978 Instituto Nacional de Cardiología p 143
24 Van Praagh R Durnin R E Jockin H Wagner H Korns M, Garabedian H Ando M and Calder A. Anatomically corrected malposition of the great arte (S-D L) Circulation 51 20 1975
25 Van Praagh R Dextrocardia mesocardia and levoc dia in Keith J Rowe R and Vlad P editors He disease in infancy and childhood New York, 19 MacMillan Publishing Company Inc p 79.
26 De la Cruz M V, Berrazueta J R Arteaga M a Attie F Rules for diagnosis of arterioventricular dis dance and spatial identification of ventricles. Cros great arteries and transposition of the great arteries Heart J 38 341 1976
27 Van Praagh R and Van Praagh S Anatomica corrected transposition of the great arteries Br Hear 29 112 1967
28 Van Praagh R Terminology of congenital heart dise (Editorial) Circulation 56 139 1977

Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978 Therefore all manuscripts must be accompanied by the following written statement signed by one author The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C V Mosby Company in the event the work is published The undersigned author warrants that the article is original is not under consideration by another journal and has not been previously published I sign for and accept responsibility for releasing this material on behalf of any and all co authors" Authors will be consulted when possible regarding republication of their material

Clinical characteristics, electrocardiographic and enzyme correlations, and long-term prognosis of patients with chest pain associated with ST depression and/or T wave inversion

John H Poehlman M D *
Mark E Silverman M D **
Atlanta Ga

The electrocardiographic distinction between transmural (TMI) and nontransmural myocardial infarction (NTMI) although not always accurate at autopsy has been used by clinicians to assess the clinical severity and prognosis following the coronary event Previously the prognosis of TMI as diagnosed by the electrocardiogram (ECG) has been considered to be graver than that of NTMI Recent reports however indicate that patients suffering NTMI may experience complications similar to TMI and a long term prognosis that is equal to or worse than TMI This retrospective study was undertaken to provide further information about the clinical course electrocardiographic and enzyme correlations and long term prognosis of patients admitted with prolonged chest discomfort and serial ST and/or T wave changes consistent with commonly used criteria for nontransmural myocardial infarction

Methods

The hospital records of 90 patients dying or discharged with the final diagnosis of nontransmural or subendocardial myocardial infarction during the period from March 1971 to November 1976 were reviewed in detail From these charts 50 patients were found to meet the following criteria

1 *Chest pain* or discomfort consistent with myocardial infarction lasting 30 minutes or more and occurring within 24 hours of admission

2 *ECG Changes* (a) New ST segment depression of the ischemic or square wave type of at least 1 0 mm occurring in two or more leads and persisting at least 24 hours and/or (b) New T wave inversion in two or more precordial or frontal plane leads persisting at least 24 hours (c) ST T or T wave evolution during hospitalization (d) No evidence by ECG of transmural infarction as defined by the development of an abnormal Q wave

3 Patients with either complete left bundle branch block or Estes criteria for probable or definite left ventricular hypertrophy were excluded ' In addition patients with electrolyte disturbances or stroke were not included

4 Patient survival for 24 hours to allow for at least two ECG s at least 24 hours apart

Prior cardiovascular history was obtained from review of physician and nurses notes a cardiovascular data base compiled on each patient on admission previous admission records physician office records and in most cases by patient interview at the time of follow up July 1978 Patients were considered to have stable angina pectoris if they had symptoms consistent with transient myocardial ischemia occurring for at least one month or more Unstable angina was

From the Department of Medicine Emory University School of Medicine and Piedmont Hospital Atlanta Ga.

Received for publication Aug. .., 19 9
Accepted for publication Oct 9 19 9

Reprint requests John H Poehlman M D 1308 Memorial D D lto Ga ,0 0

Fellow in Cardiology Emory University School of Medicine

Professor of Medicine (Cardiology) Emory University School of Medicine and Piedmont Hospital, Atlanta Ga.

0002 8 03/80/0"01/3 + 08$00 80/0

Table I Age and sex distribution of patients studied

Age (yrs)	*Male*	*Female*	*Total (%)*
40-49	2	1	3 (6)
50-59	3	2	5 (10)
60-69	11	7	18 (36)
70-79	10	10	20 (40)
80-89	1	3	4 (8)
Total (%)	27 (54)	23 (46)	50 (100)

Table II Clinical history

Historical parameter	*Number of patients*	*(%)*
Asymptomatic	10	(20)
Angina pectoris chronic stable	9	(18)
Angina Pectoris chronic unstable	21	(42)
Angina pectoris recent onset (<4 weeks)	10	(20)
History of prior myocardial infarction	22	(44)
History of congestive heart failure	8	(16)
History of hypertension	25	(50)
History of cigarette smoking (>1 pack/day)	19	(38)

as any combination of the following (a) onset of angina pectoris within one month of admission (b) episodes of angina pectoris during the month prior to admission that were more frequent more severe more easily precipitated more prolonged or that occurred at rest

Each patient was followed closely by a cardiologist a cardiology fellow a personal physician and by experienced CCU nurses A data sheet was used to compile a clinical profile of the illness and the complications as they occurred In this fashion detailed observations were made on each patient by the physicians and nurses a minimum of five times a day Twelve lead electrocardiograms were recorded at the time of admission and daily while the patient was in the coronary care unit (CCU) After discharge from the CCU the frequency was variable but all patients had at least one further electrocardiogram near the time of discharge At the time of admission the precordial electrocardiographic electrode positions were marked with indelible ink to insure reproducibility Old electrocardiograms were available for 90% of the patients either from prior admissions or from office records Blood was drawn on admission and each morning thereafter for at least three days for determination of total serum creatinine phosphokinase (CK) and total lactic dehydrogenase (LDH) enzymes A review of the emergency room and CCU records showed that none of the patients had received intramuscular injections A patient was said to have positive enzymes if the total CK and/or LDH values displayed a rise and fall and the highest value exceeded the upper limits of normal In addition the highest value had to exceed the lowest value by at least twofold[1]

Table III Clinical parameter during hospitalization

Clinical parameter	*Number of patients*	*(%)*
Uncomplicated hospital course	23	(46)
Uncomplicated hospital course	27	(54)
Congestive heart failure	16	(32)
Shock	2	(4)
Positive enzymes	37	(74)
Ventricular tachycardia	5	(10)
Ventricular fibrillation	6†	(12)

One of these patients died
†In four patients this was a terminal rhythm

Hospital course

1 Uncomplicated course Relief of pain during the first 24 hours without recurrence absence of complex atrial and/or ventricular arrhythmias absence of or only lower lobe rales and/or a ventricular gallop that disappeared

2 Complicated course Recurrent or persistent ischemic pain after the first 24 hours requiring therapy arrhythmias requiring extended periods of therapy slowly clearing persistent or recurrent congestive heart failure cardiogenic shock cardiac arrest

On follow up by review of office records subsequent hospital records or telephone interview July 1978 a patient s status was considered asymptomatic if no or rare angina had been experienced A death was considered to be of cardiovascular etiology if it was known to occur in the setting of chest pain or was sudden When circumstances surrounding the death were either unknown or not clearly related to a cardiovascu

Table IV Correlation of electrocardiographic changes, enzymes curves, and course during hospitalization and follow up

	T wave inversion		*ST depression*		*Mixed changes*		*Total*	
Incidence (% of total)	20 (40%)		12 (24%)		18 (36%)		50	
ECG changes — Limb leads alone	1		0		0		1	
ECG changes — V leads alone	5		2		2		9	
ECG changes — Both limb & V leads	14		10		16		40	
	+Enzymes	*−Enzymes*	*+Enzymes*	*−Enzymes*	*+Enzymes*	*−Enzymes*	*+Enzymes*	*−Enzymes*
Number (% of Group)	11 (55%)	9 (45%)	10 (83.3%)	2 (16.7%)	16 (88.9%)	2 (11.1%)	37 (74%)	13 (26%)
CHF at time of admission	3	3	4	0	6	0	13	3
Shock during hospitalization	0	0	1	0	1	0	2	0
Died during hospitalization	0	0	4	0	0	0	4	0
Uncomplicated hospital course	8	5	3	2	8	1	19	8
Complicated hospital course	3	4	7	0	8	1	18	5
MI after discharge	4	1	0	0	3	0	7	1
Angina during follow up	6	5	2	0	7	0	15	5
Died during follow up	5	2	2	1	8	1	15	4
CV death	4	1	0	1	6	0	10	2

lar etiology the cause of death was considered unknown. A patient was counted as having suffered subsequent *myocardial infarction (MI)* if this was documented by a review of hospital records, electrocardiograms, and enzyme studies.

Results

Population studied (Table I). There were 27 males (54%) and 23 females (46%). The majority of patients (76%) were in their sixth or seventh decades. The ages ranged from 43 to 88 years with a mean of 68.3 years and a median age of 69 years. The mean hospital stay was 17.4 days with a range of one to 43 days.

Prior cardiovascular history (Table II). Thirty patients (60%) had a history of chronic angina pectoris and ten other patients (20%) developed angina pectoris for the first time during the four weeks prior to admission. Twenty two patients (44%) related a history of prior MI, 21 of whom also had a history of chronic angina pectoris. In all 40 patients (80%) had a history of symptomatic coronary artery disease (CAD). In eight patients (16%) there was a history of CHF treated with digitalis. These eight patients also had a history of chronic angina pectoris and at least one prior MI. Excluding the 10 patients with recent onset of angina pectoris, the duration of chronic angina pectoris ranged from two months to 30 years with a mean of 6.3 years. Thirty one patients (62%) had unstable angina pectoris. In 21 (42%) it was manifested by a change in pattern of chronic angina pectoris and in ten (20%) by angina pectoris of recent (less than 4 weeks) onset.

Five of the infarctions occurred in patients who were hospitalized and recovering from recent (less than 10 days prior to MI) noncardiovascular surgery. Four of these five patients related a history of prior MI and chronic angina pectoris. Two of these five patients suffered cardiac arrest with their recurrent MI and one died. One patient in this group of five died during hospitalization because of severe heart failure.

Hospital course (Table III). Sixteen patients (32%) had CHF on admission. Six of these patients had a history of CHF, 11 had a history of at least one prior MI, and 15 had a history of chronic angina pectoris. Two patients were in shock on admission and both died during hospitalization. One patient developed shock on the second hospital day and died. There were 37 patients (74%) with positive serum CK and/or LDH enzyme curves. Two patients with positive enzymes died on the second hospital day and therefore a complete curve showing rise and fall of enzymes could not be obtained. In one of these two the CK value rose nearly twentyfold from a normal value on the second hospital day. In the other the CK value doubled by the second hospital day with an increase in the MB isoenzyme fraction. In five patients ventricular tachycardia was recorded during their CCU stay. One of these patients subsequently died in ventricular fibrillation. In the other four the rhythm spontaneously

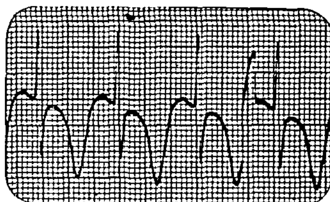


Fig 1 Lead V illustrating deep symmetrical T wave inversion pattern

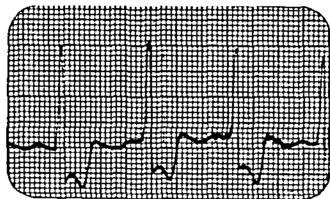


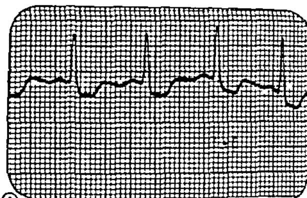
Fig 2 Lead V illustrating deep ST segement depression pattern

onverted to sinus rhythm and did not recur after reatment Six patients exhibited ventricular fibrillation In four cases this was a terminal rhythm Two patients were successfully defibrillated without subsequent cardiac arrest or death during hospitalization

Patients were retrospectively assigned to one or two hospital courses as outlined in the method section Twenty seven patients (54%) had an uncomplicated hospitalization whereas 23 (46%) had a complicated course Ten of the 19 patients who died during the follow up period of one to 82 months (mean 33 4 months) had complicated hospital courses

No patients experienced clinically detectable pulmonary or systemic emboli or pericarditis No patients developed a recognized rupture of the ventricular septum or papillary muscle

ECG changes (Table IV) In all 50 patients the ECG changes persisted for at least 24 hours and showed evolution during the hospitalization Electrocardiographic changes were frequently striking and tended to fall into three major categories



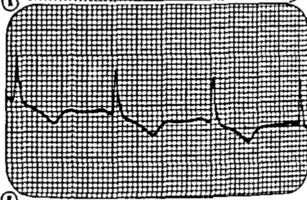


Fig 3 A and B Two examples of mixed ST and T wave changes in limb Lead II

1 Twenty patients (40%) had serial electrocardiograms with predominantly deep T wave inversion (Fig 1) These changes were often quite marked with T waves changing from upright or isoelectric to as deep as 15 mm in some precordial leads These changes were usually recorded in both the precordial and the limb leads The inverted T waves nearly always had symmetrical limbs and were frequently the most deeply inverted in the mid precordial leads Occasionally the ST segments in those leads destined for deep T wave inversion on subsequent ECGs were transiently depressed at the time of admission but usually became isoelectric within 24 hours Eleven of the 20 patients (55%) showing this particular ECG change (deep T wave inversion) had positive enzymes None of these patients died during hospitalization

2 Twelve patients (24%) had serial ECG changes primarily involving ST segment depression This was also most frequent in both the chest and limb leads Changes were often striking with ST segment depression of 8 to 10 mm in some cases (Fig 2) The ST segment was either

Table V Clinical features and hospital course in patients who died during study

	All patients	Died during hospitalization	Died during follow up: Cardiovascular causes	Died during follow up: Unknown causes	Died during follow up: Noncardiovascular causes
Number of patients	50	4 (8%)	12	5	2
Average age at time of NTMI	68.3	67.0	70.9	70.3	72.0
History of prior MI (%)	22 (44%)	4 (100%)	5 (41.7%)	4 (80%)	0
History of angina pectoris (%)	40 (80%)	4 (100%)	8 (66.7%)	5 (100%)	0
CHF with NTMI (%)	16 (32%)	1 (24%)	3 (25%)	3 (60%)	1 (50%)
+ Enzymes (%)	37 (74%)	4 (100%)	10 (83.3%)	4 (80%)	1 (50%)
T inversion pattern (%)	20 (40%)	0	5 (41.7%)	1 (20%)	1 (50%)
ST-depression pattern	12 (24%)	4 (100%)	1 (8.3%)	2 (40%)	0
Mixed pattern	18 (36%)	0	6 (50.0%)	2 (40%)	1 (50%)
Uncomplicated hospital course	27 (54%)	0	9 (75%)	0	0
Complicated hospital course	23 (46%)	4 (100%)	3 (25%)	5 (100%)	2 (100%)

Sudden death MI CHF

isoelectric or downsloping and depression occurred most frequently in the lateral precordial leads and in limb Leads 1 and aV_L. In those leads showing significant ST depression the T waves were usually inconspicuous and biphasic or slightly inverted. As with the deep T inversion pattern serial electrocardiograms showed slow resolution of these changes over a week or more. Ten of these 12 patients (83.3) had positive enzymes. All four of the patients who died during hospitalization had this ECG pattern. Two patients died on the second hospital day, one died on the sixth hospital day, and one patient died on the seventh hospital day. All four had positive enzymes, a history of prior MI, and a history of hypertension.

3. Eighteen patients (36%) had ECG changes involving both the ST segment and the T wave similar to those described above. Usually, however, the changes were much less marked than when the changes were confined to either the ST segment or the T wave alone (Fig. 3). As with the other two patterns described above this mixed pattern was found to be most frequent in both the limb leads and the chest leads. In this group 16 of the 18 patients (88.9%) had positive enzymes. None of this group died during hospitalization.

Several clinical parameters from those patients with acute infarction in hospital as well as several findings on follow up were looked at in relation to the major ECG patterns manifested with NTMI (Table IV). As noted, the four in hospital deaths all occurred in patients who had deep persistent ST depression. There was no statistical difference in the incidence of a complicated hospital course in the three groups although it tended to be lower (35%) in the group with T wave changes alone than it was in the group with ST segment changes (58%) or mixed changes (50%). There did not appear to be any relation between the post hospitalization course and the ECG changes manifested during hospitalization (Table V).

Follow up. Forty six patients survived hospitalization. One was completely lost to follow up after discharge. Two patients were lost after 16 and 40 months of follow up. The remaining 43 patients (93.5% of those discharged) were followed for one to 82 months (mean of 33.4 months and median of 33.0 months).

Among the 45 patients partially or totally followed up there were eight myocardial infarctions during follow up occurring one week to 34 months after discharge. Six of these occurred within 3 months following discharge. Of the eight patients with MI following discharge, two patients had recurrent nontransmural MI, four had documented transmural MI by electrocardiogram, one patient died in the emergency room with an extensive transmural infarction at autopsy, and one patient was hospitalized elsewhere with a diagnosis of myocardial infarction and cardiac arrest.

At the time of follow up 11 of the 24 patients (45.8%) still alive had angina pectoris. Nineteen of the 43 patients completely followed up (44%) had died during follow up. Twelve of these deaths were known to be due to cardiac causes. In five

patients the cause of death could not be determined One patient died in an automobile accident and one died from cancer of the prostate Of the 12 patients whose death was due to cardiovascular disease eight died suddenly at home Two of these 12 patients died during hospitalization for myocardial infarction (one NTMI and one TMI) and two died from refractory congestive heart failure while hospitalized The average age at the time of NTMI of the 19 patients who died posthospitalization was 70 9 years From the group of 12 patients who are known to have died from cardiovascular causes after discharge four died during the first year of follow up three died during the second year two died during the third year and three died between the fourth and sixth years of follow up The longest survivor among this group of 12 patients died 67 months after the NTMI There was a statistically significant greater incidence of both angina pectoris and myocardial infarction during follow up in those patients who manifested a positive enzyme curve during hospitalization with NTMI Similarly there was a greater incidence of death from all causes including cardiovascular death during follow up in those patients manifesting positive enzyme curves compared to those patients without positive enzyme curves (Table IV)

Discussion

Advances in the diagnosis and therapy of coronary atherosclerotic heart disease have given impetus to studies that help define the clinical characteristics and prognosis of various subsets of this disease Until recently NTMI was felt by some to represent a mild form of myocardial infarction with a relatively good prognosis The reasons for this optimistic view are unclear and may be based upon the more impressive visual impact of ST segment elevation and the development of abnormal Q waves as compared to ST segment depression and/or T wave inversion alone In fact the electrocardiogram may be deceiving since transmural infarction may occur despite ECG changes pointing to a subendocardial localization In addition the ECG may not reveal the presence of prior infarction reinfarction in areas of prior infarction or infarction in certain areas of the heart For these reasons we prefer to use a *clinical* taxonomy referring to these patients as prolonged pain with objective evidence of infarction with or without complication [1] This approach utilizes the information that is available to the clinician and helps to avoid erroneous assumptions The group can then be further defined on the basis of electrocardiographic alterations

The patients reported here represent a population defined by prolonged chest pain compatible with myocardial infarction occurring within 24 hours of admission survival for at least 24 hours to insure that the ECG changes do not suggest transmural involvement and ECG changes thought to represent nontransmural infarction. Since the majority of hospitalized patients with acute myocardial infarction who die do so within 24 hours this study is slanted towards a relatively high hospital survival group with a low incidence of cardiogenic shock The purpose of this study was to analyze this selected group in terms of hospital course enzyme correlations with ECG changes and posthospitalization prognosis Our findings are similar to other recently reported studies and suggest the following conclusions

1 NTMI occurs most often in patients with known coronary artery disease A prior history of angina pectoris and/or myocardial infarction was obtained in 80% of our patients Thirty one (62%) patients had unstable angina pectoris prior to admission and despite intensive medical therapy in most developed NTMI Other studies comparing the clinical features of TMI and NTMI have suggested that a prior history of angina pectoris is greater with NTMI

2 There was a high incidence of heart failure hypotension life threatening arrhythmias and recurrent ischemic pain during hospitalization for NTMI Five of our patients had ventricular tachycardia and six had ventricular fibrillation A third of our patients developed congestive heart failure by examination and/or chest x ray Other studies confirm that NTMI and TMI share a similar in hospital incidence of arrhythmia CHF shock and death [7]

3 There was an 8% hospital mortality rate and a high incidence of recurrent myocardial infarction and death in the next several years This compares to a hospital mortality rate of 7% in 200 consecutive patients with transmural infarctions surviving at least 24 hours after CCU admission during 1971 to 1973 at Piedmont Hospital In the present study during follow up over a mean period of 33 4 months there was a further mortality rate of 45 2% In addition 17 8% of the discharged patients in the present study suffered a subsequent myocardial infarction and in three fourths

of these patients the myocardial infarction occurred within 3 months of discharge A high mortality rate and sudden death during follow up has been a feature of other studies of NTMI[6] A study by Cannom and associates comparing the posthospital course of TMI and NTMI found that the NTMI had a higher incidence of sudden death (33% vs 15%) cardiac related mortality rate (41 6% vs 24 3%) recurrent MI (26% vs 12%) and angina pectoris (61% vs 36 2%) over a 36 month mean follow up period[1]

4 There may be a more benign *initial* course in patients with only T wave inversion Our patients with ECG changes confined primarily to deep T wave inversion had a lower incidence of enzyme elevation CHF serious ventricular arrhythmias and major problems during hospitalization although the differences were not statistically different Their hospital mortality rate was 0% as compared to four deaths (33 3%) in the group with persistent deep ST segment depression Lown and co workers have also reported 0% mortality rate in 50 patients with T wave inversion only as compared to a 27 6% mortality rate in 29 patients with ST segment depression Abbott and Scheinmann[13] also found a higher incidence of shock and death with ST depression than with T wave inversion only No statistically significant correlation was apparent between the major ECG changes manifested with the NTMI and the posthospitalization course in the present study This may be explained by other studies that show that the prognosis may be dependent upon the severity location and extent of the coronary artery obstruction and the extent of new and old myocardial damage

5 We found an over all incidence of positive enzyme curves of 74% in the 50 patients Further analysis showed that the group with T wave inversions had a 55% incidence the group with primarily ST segment depression had an 83 3% incidence and the group with the mixed ECG pattern had an 88 9% incidence of positive enzymes (Table IV) This may be explained on the basis of a smaller amount of myocardial necrosis occurring in the group with T wave inversion alone or the possibility that some patients in the group with T wave inversions did not actually suffer any myocardial necrosis This group did have fewer hospital complications and no hospital deaths however the posthospitalization course was similar to the other ECG groups Rapaport has recently discussed the problem of persistent ST T wave changes with serial enzymes remaining in the normal range He suspected that many of these patients had had small nontransmural myocardial infarctions

6 Other studies have shown that patients with NTMI usually have severe coronary artery disease[1] Recent studies of the coronary arteriograms of survivors of NTMI have found a high incidence of multivessel disease All six patients autopsied in our series had extensive coronary atherosclerosis

In summary nontransmural myocardial infarction is not a mild myocardial infarction Studies showing a similar hospital course and mortality rate for patients with TMI and NTMI support the concept that it is the extent of the coronary atherosclerosis and myocardial dysfunction from old and new infarctions rather than the ECG classification that primarily determines prognosis A recent study by Strauss and colleagues concluded that the predominant determinant of mortality was infarct size regardless of whether it was subendocardial or transmural Because of the significant incidence of further myocardial infarction and death and the documentation that severe multivessel disease is often present early coronary arteriography may be indicated This decision must be carefully considered because of the advanced age (average age 68 3 years in our study) and the unknown surgical prognosis in this group of patients A recently reported study of 28 patients with subendocardial infarction followed by saphenous vein aortocoronary bypass grafting within 3 months of the infarction has shown a 10 7% incidence of perioperative infarction a 3 6% operative mortality rate and no late deaths or recurrent infarction at a mean follow up period of 16 months This study however excluded patients over age 70 and should not be extrapolated to an older age group In another recent study reporting the long term results of 28 patients subjected to coronary bypass surgery during the acute phase of NTMI there were no hospital or late deaths during a mean follow up period of 29 months and a majority of patients demonstrated functional improvement

Summary

The clinical characteristics electrocardiographic changes and long term prognosis were studied in 50 patients suffering nontransmural myocardial infarctions It is concluded that

transmural myocardial infarcts tend to occur in older patients with known coronary atherosclerosis and these infarctions are frequently preceded by a period of unstable angina The clinical course is often complicated with congestive heart failure and other major management problems Three different groups of electrocardiographic changes were noted and all four in hospital deaths showed the same pattern of electrocardiographic changes The prognosis of patients suffering nontransmural myocardial infarctions is not good as evidenced by a death rate similar to reported patients suffering transmural myocardial infarction and a significant incidence of cardiovascular disability in those who survive

The authors wish to thank Lee Weigel for her perseverance and Lesley Gjedde and Pat Kirby for their secretarial support We also wish to thank Drs Robert C Schlant and J Willis Hurst for their help in critically reviewing this manuscript

REFERENCES

1 Horan L G., and Flowers, N C Diagnostic power of the Q wave Critical assay of its significance in both detection and localization of myocardial deficit in Schlant R C., and Hurst J W., editors Advances of Electrocardiography New York 1972 Grune & Stratton Inc., p 321 330
2 Lown B Vassaux C Hood W B Jr., Fakhro A M Kaplinsky E., and Robert G Unresolved problems in coronary care Am J Cardiol 20 494 1967
3 Friedberg C K Symposium Myocardial infarction 1972 (Part 1) Circulation 45 179 1972
4 Norris R M Brandt P W Caughey D E Lee A J and Scott P J A new coronary prognostic index Lancet 1 2 4 1969
5 Peel, A A F Semple T Wang I Lancaster W M and Dall J L A coronary prognostic index for grading the severity of infarction Br Heart J 24 745 1962
6 Madigan N P Rutherford B D and Frye R L The clinical course early prognosis and coronary anatomy of subendocardial infarction Am J Med 60 634 1976
7 Rigo P Murray M Taylor D R Weisfeldt M L., Strauss H W and Pitt B Hemodynamic and prognostic findings in patients with transmural and nontransmural infarction Circulation 51 1064 1975
8 Madias, J E Chahine R A Gorlin R and Blacklow D L A comparison of transmural and nontransmural acute myocardial infarction Circulation 49 499 1974
9 Scheinmann, M M and Abbott J A Clinical significance of transmural versus nontransmural electrocardiographic changes in patients with acute myocardial infarction Am J Med 55 602 1973
10 Cannom D S Levy W and Cohen L S The short and long term prognosis of patients with transmural and nontransmural myocardial infarction Am J Med. 61 452 1976
11 Romhilt D W and Estes E H., Jr A point score system for the ECG diagnosis of left ventricular hypertrophy AM HEART J 75 752, 1968
12 Rapaport E Serum enzymes and isoenzymes in the diagnosis of acute myocardial infarction Mod. Concepts Cardiovasc Dis 46 43 1977
13 Abbott J A and Scheinmann M M Nondiagnostic electrocardiogram in patients with acute myocardial infarction Clinical and anatomic correlation Am. J Med 55 608 1973
14 Cook R W., and Edwards J E Electrocardiographic changes in acute subendocardial infarction II Small subendocardial infarcts Circulation 18 613 1958
15 Cook R W., Edwards J E., and Pruitt R D Electrocardiographic changes in acute subendocardial infarction I Large subendocardial and large nontransmural infarcts Circulation 18 603 1958
16 Madias J E and Gorlin R The myth of acute mild myocardial infarction Ann Intern Med 86 3 4 1977
17 Hurst J W., and King S B Definitions and classifications of coronary atherosclerotic heart disease in J W Hurst R B Logue R C Schlant and N K Wenger editors The Heart ed 3 New York 19 8 McGraw Hill Book Company Inc chap 62A p 1094 1102
18 Horn H., Field L. E., Dack S and Master A M Acute coronary insufficiency Pathologic and physiologic aspects an analysis of 25 cases of subendocardial necrosis AM HEART J 40 63 1950
19 Yu P N G and Stewart J M Subendocardial myocardial infarction with special reference to the electrocardiographic changes AM HEART J 39 862, 1950
20 Levine H D and Ford R V Subendocardial infarction Report of six cases and critical survey of the literature Circulation 1 246 1950
21 Pruitt R D Klakeg C H and Chapin L E Certain clinical states and pathologic changes associated with deeply inverted T waves in the precordial electrocardiogram Circulation 11 517 1955
22. Georras C S Dahlquist E and Cutts F B Subendocardial infarction Correlation of clinical, electrocardiographic and pathologic data in 1 cases Arch. Intern. Med 111 488 1963
23 Madigan N P Rutherford B D Barnhorst D A and Danielson, G K Early saphenous vein grafting after subendocardial infarction Immediate surgical results and late prognosis Circulation 56(Suppl II) II 1 1977
24 Aintablian A Hamby R I., Weisz D Hoffman I Voleti C and Wisoff B G Results of aortocoronary bypass grafting in patients with subendocardial infarction Late follow up Am J Cardiol 42 183 1978
25 Strauss H Sobel B E and Roberts R Acute and long term prognosis in patients with transmural versus subendocardial infarction Circulation 58(Suppl. II) II 193 1978

Mexiletine in the treatment of refractory ventricular arrhythmias A report of five cases

William J Cady Pharm D
Charles S Wilson M D
Ward A Chambers M D
Richard R Miles M D
Terry L Holcslaw Ph D
Alan D Forker M D
Omaha Nebraska

Ventricular premature beats (VPB s) are the most common form of ventricular arrhythmia Because VPB s are often harbingers of more serious arrhythmias patients who are symptomatic from the VPB s and have underlying heart disease should have treatment initiated to correct the precipitating cause and/or suppress the VPB s To date initiation of antiarrhythmic therapy in the asymptomatic patient who has no evidence of heart disease is controversial

The intravenous agent that has proved to be most effective in the management of VPB s is lidocaine But it is often necessary to manage these VPB s on a chronic basis with oral medications There are several medications commercially available for this purpose Unfortunately many patients cannot tolerate these drugs or the agents are ineffective even in combination therapy in achieving adequate control Therefore it is essential that other oral agents be developed for use in patients with chronic VPB s A congener of lidocaine that can be given orally mexiletine is currently being investigated in the United States We have successfully utilized mexiletine to control chronic VPB s in the five patients described below

From the University of Nebraska Medical Center College of Pharmacy Omaha

Received for publication Nov 8 19 8

Accepted for publication Jan 15 19 9

Reprint requests Dr William J Cady University of Nebraska Medical Center College of Pharmacy 42nd and Dewey Ave Omaha Nebraska 68105

Case reports

Patient 1 L C a 59 year old Caucasian male was admitted to a local hospital after complaints of dizziness and palpitations Upon arrival he had a syncopal episode and was noted to have ventricular fibrillation (VF) which responded to DC countershock and CPR The patient had four to five of these dizzy episodes in the few days prior to admission During the hospitalization it was noted that the patient had multifocal VPB s recurrent ventricular tachycardia and Mobitz Type I second degree AV block Cardiomegaly was noted on chest roentgenogram and echocardiogram but the echo did not demonstrate any left ventricular hypertrophy Cardiac catheterization demonstrated a diffusely hypokinetic left ventricle and normal coronary arteries Therefore the diagnosis of primary myocardial disease was made The recurrent ventricular tachycardia was controlled with intravenous lidocaine The arrhythmias had been unsuccessfully controlled with therapeutic doses and combinations of quinidine 400 mg every 6 hours procainamide 750 mg every four hours disopyramide 150 mg every four hours propranolol 60 mg every four hours phenytoin 250 mg twice a day and digoxin 250 mcg every day Overdrive electrical pacing was also attempted without success A permanent epicardial pacemaker was implanted as the patient had an intrinsic ventricular rate of 44/minute without drug therapy

He was transferred to the University of Nebraska Medical Center to attempt control of his

0002 8 03/80/020181 + 04$00 40/0 © 1980 The C V Mosby Co

arrhythmias with mexiletine Mexiletine therapy was initiated with 100 mg every six hours and was subsequently increased to 400 mg every six hours due to inadequate arrhythmia control at the lower doses The maximum daily dosage recommended by the company is 1 200 mg thus this dosage exceeds the current recommendations A repeat 24 hour Holter monitor at this time showed only 1 to 3 VPB s for the 24 hour recording period It was decided that his arrhythmia was well controlled and he was discharged

Since this time he has returned to work An episode of ventricular tachycardia was noted which was quickly converted with an intravenous bolus of lidocaine and the mexiletine dosage was increased to 500 mg every six hours At the next clinic visit he was noted to have some signs suggestive of toxicity disorientation and slurred speech therefore his dosage was decreased to 400 mg every six hours and propranolol 20 mg every six hours was added to his regimen The patient s arrhythmia has been under control for the six months that he has been on the combination regimen With the exception of the manifestations of toxicity noted earlier the only adverse effect noted by this patient has been gastrointestinal irritation This has been relatively well controlled with the concomitant administration of milk and small amounts of food taken with each mexiletine dose

Patient 2 D F a 26 year old Caucasian male has had syncopal episodes with temporary vision loss since April 1977 Cardiac examination was normal A 24 hour Holter monitor was performed which showed 5 840 VPB s and recurrent episodes of ventricular tachycardia during the recording period A treadmill exercise test demonstrated an increase in VPB s with exercise Cardiac catheterization was performed which revealed mild mitral valve prolapse, hyperkinetic left ventricle and normal coronary arteries with no obstruction Intravenous lidocaine caused suppression of both the VPB s and ventricular tachycardia Quinidine 200 mg four times a day was initiated but had to be discontinued due to an acute elevation of his liver enzymes Therefore his antiarrhythmic regimen consisted of the following drugs in therapeutic doses and combinations phenytoin 400 mg three times a day procainamide 500 mg four times a day digoxin 250 mcg daily propranolol 40 mg four times daily and disopyramide 150 mg three times a day Propranolol controlled the ventricular tachycardia but not the VPB s and disopyramide was only able to somewhat suppress the VPB s Mexiletine therapy was initiated at a dosage of 200 mg every eight hours and was increased to 300 mg every eight hours due to inadequate control Arrhythmia control was documented by a treadmill exercise test and repeat 24 hour Holter monitor On followup a few VPB s were noted and propranolol 20 mg every eight hours was added This combination therapy caused complete suppression of the VPB s and ventricular tachycardia He has been on this regimen for nine months with no recurrent problems The only adverse effect has been gastric burning following each dose of mexiletine but this has been overcome by eating fruit at the time the drug was taken

Patient 3 E S a 65 year old Caucasian female was admitted for control of her VPB s Her past medical history was positive for angina pectoris mild hypertension and congestive heart failure but these were well controlled with medications at this time A 12 lead electrocardiogram did not reveal any acute changes—only nonspecific ST T changes Physical examination revealed a fourth heart sound but no elevation of jugular venous pulses or evidence of left ventricular hypertrophy A 24 hour Holter monitor demonstrated 11 520 VPB s in the 24 hour recording period Echocardiography did not demonstrate any left ventricular dysfunction or valvular disease to which the VPB s could be associated Her arrhythmia did not respond to therapeutic doses of procainamide 500 mg every six hours and only partially responded to propranolol 40 mg four times a day quinidine 324 mg twice a day disopyramide 100 mg three times a day and lidocaine 4 mg/minute Mexiletine 200 mg every eight hours was initiated with subsequent titration of the dosage to 300 mg every six hours After 48 hours on this regimen a repeat 24 hour Holter monitor was obtained which demonstrated less than 1 100 VPB s in the monitoring period which was considered to be a satisfactory response

On follow up the patient noted occasional dizziness and lightheadedness This was thought to be due to the mexiletine and the dose was decreased to 300 mg every eight hours with resolution of this problem Follow up at the three

month interval demonstrated adequate control of the arrhythmia as no VPB s were noted on the 12 lead ECG or by the patient She had a syncopal episode one week prior to the three month evaluation and was hospitalized in her home town The etiology of the syncopal episode was not determined She has been maintained on the current regimen for 5 months with no further syncopal episodes or side effects

Patient 4 I M a 53 year old Caucasian male had a positive history for hypertension and angina pectoris His hypertension was well controlled with hydrochlorothiazide and angina pectoris was controlled with propranolol Electrocardiographic examination revealed an old anterolateral infarction and left ventricular hypertrophy A treadmill exercise test caused him to have ventricular bigeminy A 24 hour ambulatory electrocardiogram revealed multifocal VPB s 43 200 by computer count Control of the arrhythmia was attempted with quinidine 200 mg every eight hours and propranolol 40 mg four times a day but was not successful Mexiletine therapy 200 mg every eight hours was initiated The patient was placed on a treadmill after 48 hours of mexiletine therapy with only an occasional atrial premature contraction noted On the three month and six month follow ups no VPB s were noted on a 12 lead ECG and the patient had not noted any extra beats The patient has not noticed any adverse effects and has resumed some of his previous farm work

Patient 5 K G a 50 year old Caucasian male had experienced an anteroseptal myocardial *infarction six months prior to this hospitalization* In the interim control of the VPB s and recurrent ventricular tachycardia was attempted with propranolol 40 mg every six hours in divided doses Ventricular tachycardia was controlled with propranolol but not the VPB s Mexiletine therapy was initiated at a dosage of 200 mg every eight hours with subsequent control of the arrhythmia At the one month evaluation VPB s were noted by the patient and on a 12 lead electrocardiogram The mexiletine dose was increased to 300 mg every eight hours Follow up at four months showed the arrhythmia to be well controlled by ECG analysis and by the patient s subjective findings with no adverse effects noted Recently while riding his exercise bicycle he suddenly died Because the incident was unwitnessed the exact cause of death was not determined It was suspected to be due to ventricular fibrillation that may or may not have been secondary to another myocardial infarction

Discussion

Mexiletine is an antiarrhythmic agent belonging to the Group II class It is structurally related to lidocaine and possesses antiarrhythmic action analagous to lidocaine and phenytoin [1] It appears that its potency on isolated tissues is between that of phenytoin and lidocaine [1] Prescott and co workers have demonstrated that approximately 88% of a dose of mexiletine is absorbed into the systemic circulation The drug is widely distributed in the body volume of distribution approximating 9 47 L/Kg and obeys a three compartment pharmacokinetic model Elimination is primarily by liver metabolism with approximately 8% eliminated in the urine as unchanged drug with renal elimination being dependent upon the pH of the urine [3] With alkalinization there is a decreased elimination of the drug but this does not appear to be clinically significant with normal urine pH [3]

The dosage range commonly employed is 200 to 400 mg every eight hours [6] With the exception of patient No 1 all the patients reported here have been maintained in this dosage range With the exception of patient No 2 all of the patients have had satisfactory arrhythmia control with only mexiletine The mexiletine dosage in patient No 1 had to be decreased to control the symptoms of toxicity At this time propranolol was added for control of his arrhythmias

The side effects attributed most frequently to mexiletine are tremor nausea dyspepsia and dizziness [4,7] On long term follow up Campbell and colleagues noted that 54% of their patients had adverse effects secondary to mexiletine with 31% being classified as severe This group noted that the severity of adverse reactions increased with increasing plasma mexiletine concentrations The gastrointestinal side effects appear not to be related to drug concentration This is evidenced by the work of others and by patients No 1 and 2 in our series These patients had some gastrointestinal discomfort soon after the mexiletine was initiated and this continued throughout therapy as the dosage was increased Patient No 3 had occasional dizziness and lightheadedness

Table I

Patient number	Daily dose (mg)	Plasma concentration (mcg/ml)
1	1600 mg	2 58
3	1200 mg	1 0
4	600 mg	0 97
5	600 mg	1 2

that became apparent only after intensive questioning Her dosage was decreased with alleviation of these effects Throughout the follow up period on these patients 8 to 12 months no abnormalities have been noted on repeated laboratory examinations for any patient

The therapeutic plasma concentration range for optimal suppression of ventricular arrhythmias by mexiletine is 0 5 to 2 mcg/ml[illegible] At the time the patients were started on mexiletine therapy, we did not have a functioning assay procedure for mexiletine Our dosing regimens were determined by the clinical response of the patients and by the occurrence of any adverse effects In a retrospective fashion we have determined the plasma concentrations on four of the five patients Blood was obtained by venipuncture and was centrifuged The plasma was then stored in a frozen state The plasma concentrations were determined by the method of Kelly[9] with modifications for use in our laboratory All levels reflect the minimum plasma concentration at steady state (see Table I) As can be readily seen all of these plasma concentrations with the exception of patient No 1 were within the therapeutic range From the patient descriptions it can be readily seen that the arrhythmias were well controlled with these plasma concentrations The arrhythmias were not satisfactorily controlled with mexiletine alone in patient No 2 and this necessitated the addition of propranolol to his therapy The arrhythmias of patient No 1 were controlled with mexiletine only but due to the reduction in dosage for control of his side effects it was decided to add propranolol to his regimen Inadequate arrhythmia control in patient No 2 may have been due to plasma mexiletine concentrations below the therapeutic range This is doubtful because it has been demonstrated that mexiletine dosages of 300 mg every eight hours provide therapeutic plasma concentrations[illegible, 10] It definitely was not the case in patient No 1 as his plasma mexiletine concentration was above the therapeutic range (see Table I)

Conclusion

From the preliminary data on five patients it appears that mexiletine is a potentially useful antiarrhythmic agent Because we were able to control ventricular arrhythmias refractory to therapeutic doses of conventional antiarrhythmic therapy the potential for the use of this agent is increased As no severe adverse effects were noted that necessitated withdrawal of this agent it appears quite safe It is realized that the patient population is small but the success noted with mexiletine is very suggestive of the potential benefit of this medication Only through further use of this agent will the total benefits be realized

We would like to thank Boehringer Ingelheim Ltd for providing us with the mexiletine capsules

REFERENCES

1 Danneberg P B and Shelley J H The pharmacology of mexiletine Postgrad Med J 53(Supp 1) 25 1977
2 Prescott L F Pottage A and Clements J A Absorption distribution and elimination of mexiletine Postgrad Med J 53(Supp 1) 50 1977
3 Kaye C M Kiddie M A and Turner P Variable pharmacokinetics of mexiletine Postgrad Med J 53(Supp 1) 56 1977
4 Campbell N P S Kelly J G Shanks R G and Adgey A A J Long term oral antiarrhythmic therapy with mexiletine Postgrad Med J 53(Supp 1) 143 1977
5 Campbell R W F, Talbot R G Julian D G and Prescott L F Long term treatment of ventricular arrhythmias with oral mexiletine Postgrad Med J 53(Supp 1) 146 1977
6 Talbot R G Julian D G and Prescott L F Long term treatment of ventricular arrhythmias with oral mexiletine AM HEART J 91 58 1976
7 Campbell N P S Pantridge J F and Adgey A A J Mexiletine in the management of ventricular dysrhythmias Eur J Cardiol 6 245 1977
8 Campbell N P S Pantridge J F and Adgey A A J Long term oral antiarrhythmic therapy with mexiletine Br Heart J 40 796 1978
9 Kelly J G Measurement of plasma mexiletine concentrations Postgrad Med J 53(Supp 1) 48 1977
10 Campbell N P S Kelly J G Adgey A A J and Shanks R G The clinical pharmacology of mexiletine Br J Clin Pharmacol 6 103 1978

Experimental and laboratory reports

Atrial standstill, myocarditis and destruction of cardiac conduction system Clinicopathologic correlation in a dog

Karim Jeraj B V Sc *
Phillip N Ogburn D V M Ph D *
William D Edwards M D **
Jesse E Edwards M D * *
St Paul and Minneapolis Minn

Atrial standstill is a condition in which the atria as observed electrocardiographically and cineangiographically do not function[1] P waves are not observed in any lead of the electrocardiogram (ECG)[1] and an atrial electrogram cannot be recorded from an electrode either in contact with the atria or placed within the atrial chambers The atria cannot be paced through the electrodes in contact with it[2] A slow regular ventricular rhythm is observed which is either AV junctional or ventricular in origin[4]

Three forms of atrial standstill are recognized (1) temporary atrial standstill is seen with sinus bradycardia digitalis toxicity quinidine toxicity carbon dioxide poisoning hyperkalemia and during or after open heart surgery[1] (2) terminal atrial standstill is observed with terminal sinus arrest following myocardial infarction—atrial activity ceases prior to ventricular arrest and death[1,3] and (3) permanent atrial standstill is an irreversible condition which is associated with extensive atrial disease

Permanent atrial standstill is a rare condition in humans. Two cases of fascioscapulohumeral muscular dystrophy have been observed to have permanent atrial standstill[1,4] In another family with myocardial disease one member had amyloid infiltration in the right atrial appendage which was interpreted as the cause of permanent atrial standstill[2]

Permanent atrial standstill has not been described in a dog although temporary atrial standstill has been observed in dogs with hyperkalemia This report describes the clinical electrocardiographic radiographic and pathologic features of atrial standstill in a dog

Case report

A 10 month old female Springer spaniel weighing 18 kilograms with a history of ascites of unknown origin was referred to the Veterinary Teaching Hospital at the University of Minnesota Two months prior to presentation the patient had pancreatitis which responded to therapy The owner had not observed any exercise intolerance or syncopal attacks in the dog

Physical examination revealed a slightly thin dog of normal stature She was alert and active The mucous membranes were pink Femoral pulse was strong and regular Both the pulse and heart rate were 62/minute Heart and lung sounds were normal but no jugular pulse was observed Abdominal organs could not be

From the Department of Small Animal Medicine College of Veterinary Medicine University of Minnesota, and the Department of Pathology United Hospitals Miller Division St Paul, Minn and the Department of Pathology College of Medicine University of Minnesota Minneapolis.

This study was supported by Public Health Service Research Grant R01HL05694 from the National Heart, Lung and Blood Institute

Received for publication Sept 5 19 8

Accepted for publication Nov 20 19 8

Reprint requests Karim Jeraj Department of Small Animal Medicine College of Veterinary Medicine University of Minnesota St Paul, Minn 55108

*The Department of Small Animal Medicine College of Veterinary Medicine University of Minnesota St Paul, Minn

**The Department of Pathology United Hospitals, Miller Division, St Paul, Minn. and Department of Pathology College of Medicine University of Minnesota Minneapolis Minn

***The Department of Pathology United Hospitals, Miller Division, St Paul Minn

0002 8703/80/020185 + 08$00 80/0 © 1980 The C V Mosby Co

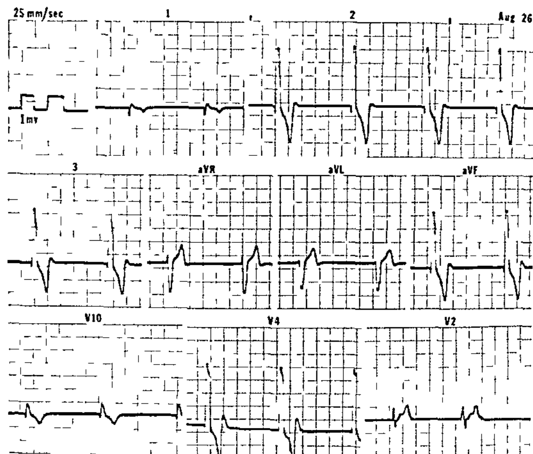


Fig 1 Standard ECG recorded from a dog with atrial standstill A P wave is not observed in any lead and a regular idioventricular rhythm with beats/minute is noted

palpated because of ascites A complete blood count and urinalysis were normal Serum potassium concentration was high normal (4 9 mEq / L) but the ratio of potassium to sodium (1 30 8) was normal Serum globulin concentration was low normal (2 2 Gm /dl) while the serum albumin concentration was normal Abdominal paracentesis showed the peritoneal fluid to be a modified transudate Cardiomegaly with slight enlargement of the pulmonary vessels was observed on thoracic radiographs There was no evidence of pulmonary edema

P waves were not observed in any lead of the initial electrocardiogram (Fig 1) The ventricular rate was 60/minute and the rhythm was regular The RR interval was 1 16 seconds and the QRS complex was 0 10 sec in duration 0 04 sec beyond normal limits The R wave amplitude was 4 6 millivolts The mean electrical axis was 91 degrees in the frontal plane The ECG was interpreted as atrial standstill characterized by bradycardia and a regular ventricular rhythm

No increase in heart rate was observed following intravenous (IV) administration of 1 0 mg of atropine sulphate (Fig 2) Administration of an IV bolus of 0 01 mg of isoproterenol hydrochloride* caused an increase in ventricular rate but still no atrial activity was observed (Fig 3) Pacemaker activity shifted from the original ventricular site to at least three other pacemaker foci Within 75 seconds the rhythm and the pacemaker activity returned to the original rhythm and pacemaker site The same response was observed subsequent to a second IV bolus injection of 0 01 mg isoproterenol hydrochloride

During anesthetic induction for cardiac catheterization and intra atrial recording the patient developed a severe arrhythmia with multifocal ventricular pacemaker sites Because of the risk the study was aborted and the patient was allowed to recover from anesthesia The patient

*Isuprel Winthrop Laboratories Division of Sterling Drug Inc, New York NY 10016

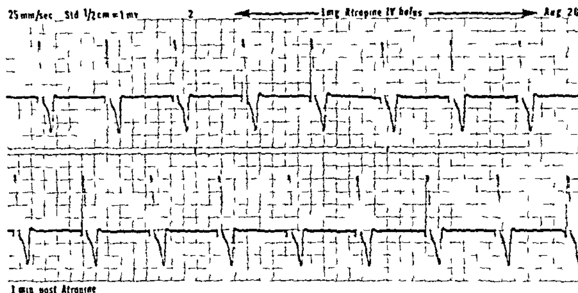


Fig. 2. Lead II recorded during intravenous injection of 1.0 mg. atropine. No change in rate or rhythm was observed one minute after completion of the injection.

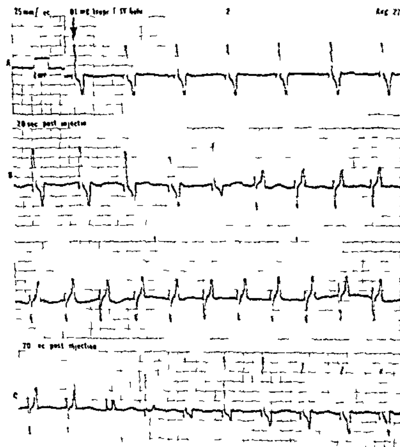


Fig. 3. Lead II recorded during intravenous injection of *0.01 mg.* of isoproterenol hydrochloride *(arrow)*. Pacemaker activity shifted from original locus and returned to its original site after 70 seconds. The pacemaker site shifted at least three times.

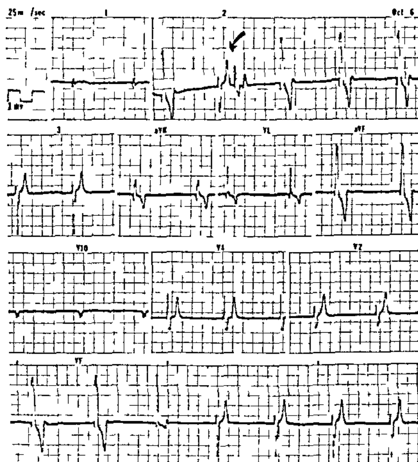


Fig 4 A P wave is not observed in any lead Idioventricular rhythm with shifting of the pacemaker locus is observed in Leads II and aV_F A premature ventricular contraction is observed in Lead II *(arrow)*



Fig 5 A and B Gross cardiac specimen *A* Marked right ventricular dilatation and mottling of myocardium *B* Left ventricular hypertrophy and mild chamber dilatation

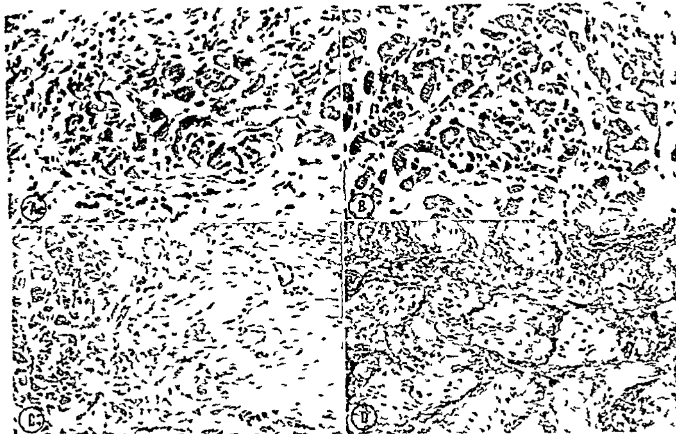


Fig 6 A through D Chronic active myocarditis *A* and *B* Active lesions of left ventricular free wall *(A)* and ventricular septum *(B)* showing extensive lymphocytic infiltrates and focal necrosis of individual myocardial cells (Both hematoxylin and eosin original magnification ×280) *C* Healing lesion of right ventricular free wall, showing lymphocytic infiltrate and ingrowth of fibroblasts (Hematoxylin and eosin original magnification ×140) *D* Healed lesion of right atrium showing patchy interstitial fibrosis (Hematoxylin and eosin original magnification ×70)

was discharged on 50 mg of furosemide† per day and low salt diet

Reexamination five weeks later showed that the patient had gained 1 kilogram in weight and the degree of ascites was less marked Pulse and heart rate were 48/minute A Grade 2/6 short systolic murmur was present and was best heard at the third right intercostal space P waves were not observed in any lead of the ECG The site of pacemaker activity was changing quite frequently and premature ventricular contractions were noted (Fig 4) The patient's physical condition appeared unchanged but the ECG indicated that the rhythm was deteriorating The patient died suddenly before a rescheduled cardiac catheterization and pacemaker implantation could be performed

Gross findings The heart at necropsy was enlarged due both to myocardial hypertrophy and to chamber dilatation The cardiac mass was 145 grams The right atrium and ventricle were markedly dilated (Fig 5a) whereas the left ventricle was only moderately dilated and the left atrium was of normal size (Fig 5*b*)

The myocardium of all chambers was focally mottled the involved areas ranging from yellow tan to gray white The yellow tan foci were generally soft while the gray white areas tended to be firm

The tricuspid and pulmonary anuli were dilated while the left sided valves were normal The coronary arteries were normal and no congenital anomalies were present

†Lasix National Laboratories Corp Subsidiary of American Hoechst Corp Somerville N.J 088 6



Fig 7 A and B Myocarditis involving sinus node *A* Normal sinus nodal artery and healed lesion showing fibrous obliteration of adjacent sinus node (Elastic van Gieson stain original magnification ×70) *B* Active lesion showing extensive lymphocytic infiltration of paranodal vagal ganglion (Hematoxylin and eosin original magnification ×140)

Microscopic findings Chronic active myocarditis was present and was extensive involving 50 to 60 per cent of each tissue section Although these lesions individually comprised relatively small foci they often coalesced to form larger conglomerate lesions

The foci of myocarditis varied in age ranging from active to healed lesions In areas of active myocarditis the lesions were those of acute myocardial necrosis associated with leukocytic infiltrate (Fig *6a* and *6b*) The infiltrate was composed primarily of lymphocytes although neutrophils were frequently present and plasma cells were occasionally encountered Areas of healing myocarditis were characterized by infiltrates of macrophages and lymphocytes neovascularization and ingrowth of fibroblasts (Fig *6c*) Foci of healed myocarditis were represented by vascular collagen scars (Fig *6d*)

The cardiac conduction system was also extensively involved by the destructive myocardial lesions described above Although the sinus nodal artery was normal no remnants of sinus nodal tissue were identified The region of the sinus node was replaced by either dense collagen or fibroadipose tissue (Fig *7a*) Paranodal vagal ganglia were often edematous and involved with a lymphocytic infiltrate (Fig *7b*)

Fascicles of atrial myocardial cells adjacent to the sinus node and to the AV node were often acutely necrotic These fiber tracts probably represented the proximal and distal portions of the so called internodal tracts

The AV nodal artery was normal However the AV node and AV bundle were involved by healed myocarditis and were totally replaced by fibrovascular adipose tissue (Fig *8a* and *8b*) The proximal one third of the left bundle branch was also involved by focal replacement by adipose tissue (Fig *8c*) Microfocal areas of acute necrosis were present at all levels of the left bundle branch The right bundle branch was not included in the planes of section

The extramural coronary arteries were normal and occasional intramural branches had medial thickening Although numerous coronary arterial branches were surrounded by foci of active inflammation an arteritis was not present

Discussion

The criteria for establishing the diagnosis of atrial standstill are (1) absence of P waves on ECG (2) absence of P waves on intra atrial electrograms (3) absence of A waves on right atrial pressure recordings (4) absence of atrial mobility as observed by fluoroscopy (5) inability to electrically stimulate the atria and (6) presence of regular ventricular rhythm[1] Our patient had absence of P waves in all ECG leads and had a regular ventricular rhythm Since intraatrial electrogram and pressures were not recorded the possibility of a retrograde P waves in the QRS complex or T wave and atrial contraction cannot be excluded Vagolysis with atropine had no observable effect on the ECG indicating that sinus inhibition by autonomic factors was not responsible for sinus arrest Permanent failure of the sinus node was excluded as a sole cause

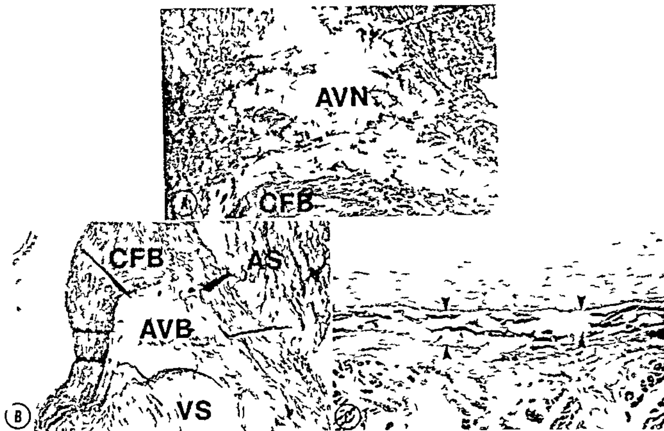


Fig. 8. A through C. Myocarditis involving atrioventricular conduction system. *A* and *B*, Healed lesions of anticipated sites of AV node *(A)* and AV bundle *(B)* showing total replacement by fibroadipose tissue (Both Elastic van Gieson stain, original magnification ×28). *C*, Healed lesion of left bundle branch *(arrow)* showing focal partial replacement by adipose tissue (Hematoxylin and eosin, original magnification ×70). *AS* = atrial septum; *AVB* = AV bundle; *AVN* = AV node; *CFB* = central fibrous body; *VS* = ventricular septum.

because there was no electrocardiographic evidence of other supraventricular sites of pacemaker activity nor was retrograde activation of the atria observed. The fact that the QRS complex was 0.04 sec. longer than normal suggested that the pacemaker locus was of bundle branch origin rather than from the AV junctional tissue. Because of the orientation of the mean electrical axis, a right bundle locus was most probable. Although absence of P waves on the ECG is also seen in sinoventricular (SV) conduction secondary to hyperkalemia, we excluded the probability of SV conduction in our patient on the basis of the normal serum potassium-sodium ratio. The possible presence of isoelectric P waves or atrial fibrillation of high frequency and low amplitude cannot be absolutely excluded; however, absence of P waves in all ECG leads and in all recordings, the regular RR interval, and the slow heart rate would tend to rule this out.

After administration of isoproterenol hydrochloride, the pacemaker site changed from its original locus. This is probably an effect of the drug, since pacemaker activity soon returned to its original site. Isoproterenol hydrochloride increased ventricular rate but did not restore atrial activity because the atria were extensively diseased and refractory to stimuli. In contrast, in atrial quiescence after open heart surgery, isoproterenol hydrochloride restores normal atrial activity by hyperpolarization of the resting membrane potential.

In this case the clinical findings correlated exceptionally well with the pathologic findings. The patient had an extensive chronic active myocarditis. The sinus node was obliterated by fibrous tissue, and paranodal vagal ganglia had lymphocytic infiltrates. The AV node and AV bundle were totally replaced by fibroadipose tissue, and the proximal third of the left bundle

branch was partially destroyed. Atrial myocardium was extensively scarred and had multiple areas of recent necrosis. Permanent atrial standstill was therefore associated with widespread lesions of the atria and the cardiac conduction system, and the functional pacemaker probably originated in the ventricles.

The finding common to all cases of permanent atrial standstill appears to be pathologic involvement of the atria. It has been observed that endocardial fibrosis and myocardial infarction will raise the stimulation threshold for myocardium, thus partially explaining why the diseased atrium is refractory to internal and external stimuli.[5]

Summary

A case of permanent atrial standstill is described in a 10 month old dog with ascites as a presenting complaint. The patient had absence of P waves in all leads in numerous ECG's and had a regular idioventricular rhythm. Pathologically, the patient had multiple areas of atrial and ventricular myocardial necrosis and fibrosis with chronic active myocarditis and obliteration of the SA and AV node and AV bundle.

REFERENCES

1. Bloomfield D A and Sinclair Smith B C Persistent atrial paralysis Am J Med 39 335 1965
2. Rosen K M Shahbuden R H Gunnar R M and Lev M Transient and permanent atrial standstill with His bundle recordings Circulation 44 220 1971
3. Waldo A L Vitikainen K J Kaiser G A Bowman F O Jr and Malm J R Atrial standstill secondary to atrial inexcitability (Atrial Quiescence) Circulation 45 690 1972
4. Combs D T Bellaci H F Shively H H and Gregoralos G Persistent atrial standstill Am J Med 56 231 1974
5. Patton R D Damato A N Berkowitz W D Lau S H and Stein E The electrically silent right atrium J Electrocardiol 3 239 1970
6. Wada M Takada E and Mise J A case report of atrial standstill Jap Circ J 30 543 1966
7. Harrison W H and Derrie J R Atrial standstill, Angiology 20 610 1969
8. Baldwin B J Talley R C Johnson C and Nutter D O Permanent paralysis of the atrium in a patient with fascioscapulohumeral muscular dystrophy Am J Cardiol 31 649 1973
9. Allensworth D C Rice D J and Lowe G W Persistent atrial standstill in a family with myocardial disease Am J Med 47 775 1969
10. Bolton G R Handbook of canine electrocardiography Philadelphia 1976 W B Saunders Company
11. Messinger W J and Mitkinson A M Permanent atrial standstill Arch Intern Med 124 711 1969

Depression of intramyocardial oxyhemoglobin dissociation by angiographic contrast media

David S Sheps M D
Bruce F Cameron M D Ph D *
Stephen M Mallon M D
Leonard S Sommer M D
William C Lo A S
Donald R Harkness M D
Robert J Myerburg M D
Miami Fla

Several potentially deleterious effects of contrast material have been described in the past decade [1-6] These have included effects of the injection of a hyperviscous and hypertonic solution on the size and shape of red cells certain hemodynamic and electrocardiographic changes a tendency to acidosis and a depression of blood calcium levels The production of acidosis by the injection of water soluble contrast materials has been clearly demonstrated However the significance of this finding upon oxygen delivery by red blood cells has been questioned When oxygen delivery is described in terms of P50 that value is expressed either as P50 at pH 7 4 or P50 in vivo Usually plasma pH adequately reflects the intra red blood cell pH throughout the physiologic range However angiographic contrast medium has been shown to alter the red blood cell pH gradient Therefore in this situation plasma does not reflect intra red blood cell pH Previous workers have measured intra red blood cell pH after the addition of contrast medium with differing results

From the Divisions of Cardiology and Hematology Department of Medicine University of Miami School of Medicine and the Papanicolaou Cancer Research Institute Miami, Fla

Supported by Florida Heart Association Grant No 5 AG 213

Received for publication Sept 25 19 8

Accepted for publication Dec 2 1978

Reprint requests David S Sheps, M D Associate Professor of Medicine Division of Cardiology School of Medicine The University of North Carolina at Chapel Hill, 349 Clinical Science Bldg 229H Chapel Hill N C 2 514

*Dr Cameron is an Established Investigator of the American Heart Association

The purpose of this study was to examine the effects of contrast medium in an experimental system where extracellular pH was kept constant using a highly buffered red blood cell solution Thus all P50 s were measured under the same conditions (pH 7 4 PCO 40 and temperature 37° C) and any changes seen would therefore directly reflect changes in intra red blood cell pH In addition the effect of contrast medium on the red cell pH gradient was examined anerobically It has previously been shown that contrast media do not alter red blood cell 2 3 DPG [3] which is the only other known explanation for acute changes in P50 in this system

In addition to the in vitro studies in vivo studies were performed on blood drawn simultaneously from the coronary sinus and peripheral arterial system prior to and one minute and five minutes after selective injection of the left coronary artery with contrast material

Methods

In vitro studies Blood was drawn from the antecubital vein of normal volunteers into tubes containing sodium heparin Methylglucamine 3 5 diacetamido 2 4 6 triiodobenzoate 66% aqueous *solution (Renografin 76)* was added to blood in concentrations varying from 02 to 08c c /c c blood and incubated for a constant time interval prior to measurement of P50 The effect of variation of incubation time from one minute to 30 minutes was evaluated at a Renografin concentration of 06c c /c c blood

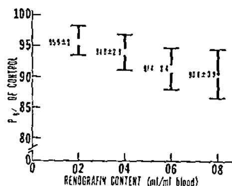


Fig 1 P_{50} after incubation with Renografin at various concentrations as shown All samples were incubated at a constant time interval of 30 minutes Results are expressed as percentage of control values (without Renografin)

Table I Red blood cell pH gradients (Plasma pH–Intraerythrocyte pH) in the control state and after 30 minutes of incubation with Renografin 06 c c /c c blood

	Control	Renografin
	0 24	0 07
	0 20	0 05
	0 20	0 08
	0 21	0 05
	0 20	0 06
	0 20	−0 03
	0 20	−0 02
Mean	0 207	0 037
Std dev	0 015	0 044
T = 11 02		
P < 0001		

Blood hemoglobin was measured with an IL 182 cooximeter

Blood oxygen dissociation curves were obtained by a modification of the method of Longmuir and Chow The curve was measured at PCO 40 pH 7 4 and 37 C on whole cell suspensions in 0 16 M sodium phosphate buffer in a 30 c c closed cell Buffers and blood samples were thoroughly equilibrated with a gas mixture containing 19 6% oxygen prior to introduction into the chamber The cell suspensions were deoxygenated by beef heart mitochondrial succinate respiration (without CO production) and the PO was measured with a membrane type oxygen electrode (YSI model 53 oxygen monitor) The oxygen signal was continuously recorded on a Kip and Zonen BD 9 recorder All curves were measured in duplicate and duplicate determinations on the same sample agreed to within ± 0 25 mm Hg

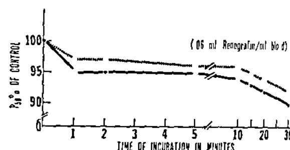


Fig 2 Effect of variation of incubation time on P_{50} with a constant concentration of 0 06 ml Renografin/ml blood P_{50}s are expressed as percentage change from control (without Renografin)

Red cell and plasma pH s were measured using an IL 213 blood gas analyzer at 37° C The red cell lysate was obtained by the freeze thaw technique PH gradients were therefore obtained across the red cell membrane in the control sta and after incubation with Renografin for minutes (06 c c Renografin/c c blood) 37° C

In vivo studies Eleven adult patients who w undergoing cardiac catheterization and select coronary arteriography were studied Arter catheters were introduced percutaneou through the femoral artery and venous cathet via a cutdown into the basilic vein The venc catheter was positioned in the proximal corona sinus The position was verified by a combinati of the fluoroscopic location and by the low ox gen saturation In eight patients studies we performed approximately ten minutes after l ventriculography In three patients studies we performed prior to left ventriculography

Prior to the first coronary injection contr samples were obtained from the proximal cor nary sinus and the central aorta Contrast mat rial was then selectively injected into the le coronary artery (approximately 6 to 12 ml over to 4 seconds) One minute and five minutes aft injection repeat blood samples were obtain from the proximal coronary sinus and the centr aorta Blood samples were cooled on ice ar oxyhemoglobin dissociation curves and P50 we determined in duplicate within twelve hours

Results

Effect of Renografin on blood P50 in vitro Th effects of Renografin on whole blood P_{50} concentrations (as outlined above) which woul be attained during cardiac catheterization we studied on blood samples drawn from eigh

Table II. Differences in P50 between coronary sinus and aorta before and after left coronary arteriography

Control			1 Minute			5 Minute		
CS	*Ao*	*Δ (CS Ao)*	*CS*	*Ao*	*Δ (CS Ao)*	*CS*	*Ao*	*Δ(CS Ao)*
29.86	—	—	28.46	29.71	−1.25	29.08	29.71	−.63
28.08	28.58	−.50	26.77	29.23	−2.46	26.28	28.25	−1.97
26.63	26.62	.01	25.92	—	—	26.91	27.19	.28
27.43	28.53	−1.10	28.84	30.40	−1.56	26.19	27.12	−.93
26.11	26.28	−.1	25.77	26.44	−.67	26.27	26.61	−.34
25.56	25.56	0	22.56	22.83	−.27	23.11	23.11	0
25.78	25.78	0	25.30	26.90	−1.60	25.23	25.51	−.28
28.93	28.57	.36	28.57	28.21	.36	29.11	29.11	0
27.30 ±	27.13 ±	−.20 ±	26.52 ±	27.67 ±	−1.06*	26.52 ±	27.07 ±	−.55 ±
1.56	1.37	.47	2.19	2.58	.94	1.96	2.10	.65
SEM .55	SEM .52	SEM .18	SEM .75	SEM .97	SEM .36	SEM .69	SEM .74	SEM .23

*Significant $p < 0.01$.

Abbreviations: CS = coronary sinus; Ao = aorta; Δ = difference of aorta from coronary sinus; SEM = standard error of the mean.

patients. For this series of experiments all blood samples were incubated with Renografin at a constant time interval of 30 minutes. The average blood Renografin concentration attained during angiography was estimated at 0.2 to 0.4 c.c. Renografin/c.c. blood. This is based on an average total dose of 100 to 200 c.c. of contrast at an average blood volume of 5 liters. Concentration added in vitro ranged from 0.2 to 0.8 c.c. Renografin/c.c. blood in all eight patients. The results are depicted in Fig. 1 as percentage decrease at each concentration when compared to the control P50. As shown in Fig. 1, the P50 progressively decreased throughout the range of concentrations studied. In two patients in whom higher concentrations were studied, P50 decreased even further. The changes from control values were significant ($p < 0.01$) by Student's t test for Renografin concentration up to 0.8 ml./c.c. blood.

The effect of the time of incubation of Renografin with blood on P50 was studied at a dose of 0.6 c.c. Renografin/c.c. blood. The time of incubation refers to the time interval prior to introduction of the blood sample into the closed cell. Results of variation of incubation time are shown in Fig. 2. In both patients studied, a significant decrease in P50 was seen at one minute incubation. This remained constant up to ten minutes of incubation beyond which point there were further decreases at 15, 20, and 30 minutes of incubation. Although the absolute decrease at one minute was only 3 to 5% of the control value, this represented a change of .7 mm. Hg which is well beyond our range of reproducibility on the same blood sample (i.e., ± 0.25 mm. Hg).

The effects of Renografin 0.6 c.c./c.c. blood on the red blood cell transmembrane pH gradient were studied in vitro in seven normal subjects. The differences between plasma and intraerythrocytic pH were compared in the control state and after 30 minutes of incubation with Renografin. The addition of Renografin decreased the plasma pH and the difference between plasma and intraerythrocytic pH (Table I). The mean pH gradient was 0.21 ± .01 prior to the addition of Renografin. The gradient after incubation with Renografin was .04 ± .04, $p < .0001$.

In vivo effects of Renografin. Control samples were simultaneously obtained from the proximal coronary sinus and central aorta and repeat samples were obtained at one minute and five minutes following injection of the left coronary artery in the 11 patients studied. In eight patients these determinations were performed after left ventriculography and in three they were performed prior to left ventriculography. The results in the initial group of eight patients are shown in Table II. There is no significant difference between P50's from coronary sinus or aorta in the control period. At one minute after left coronary injection the decrease of coronary sinus as compared to aortic P50 is significant ($p < .01$, Student's t test). This difference is reduced by five minutes post injection when values approach the control state.

When the coronary arteries were injected prior to left ventriculography there was no difference between simultaneous coronary sinus or aortic samples prior to injection or one minute or five minutes after injection

Discussion

Intravascular injection of radiographic contrast material results in a complex series of potentially deleterious effects Most of these effects have been attribued to the contrast material s hypertonicity and high viscosity A lowering of ionized calcium levels has been described secondary to angiographic contrast material which may be implicated in cases of hypotension secondary to contrast injection [8]

Initially the acidosis secondary to contrast material was thought to affect oxyhemoglobin dissociation [3] but recently it has been stated that there is no effect on oxyhemoglobin dissociation since intra red blood cell pH is not affected by angiographic contrast media Instead it was stated contrast causes an extrusion of hydrogen ions from the red cell [9]

The results of this study are in agreement with that of Lichtman and associates referred to above The decreased P50 seen in our in vitro and *in vivo studies secondary to contrast material* is explained as follows The contrast medium (Renografin 76) is a salt of an impenetrable anion and by balancing negative ions within the red cell alters the transmembrane ionic charge gradient (see Table I) When the red cell interior is strongly buffered with respect to the suspending medium the result is a relative acidification of the medium without change in intracellular pH, when the suspending medium is strongly buffered as in our studies the reduction of the pH gradient will result in an increase in intracellular pH The P50 of the blood then decreases due to the Bohr effect when compared to the same blood P50 prior to addition of contrast medium *with an intra red blood cell pH of 7 2* We and others have shown that this effect is both dosage and time dependent

The exact situation in vivo is not known and is probably dependent upon blood flow and relative buffering capacity of intra and extra red blood cell spaces The equilibrium studies of Lichtman and associates are at one extreme where the entire pH change is extracellular The red blood cell suspension system that we have examined is at the other extreme where the entire change is intracellular The actual situation in vivo would depend on the relative buffering capacity of intra and extra red blood cell spaces

In areas of rapid blood flow the changes *described are of little consequence since the dye is* rapidly diluted However in areas of myocardium distal to a critical coronary lesion these effects may take on more significance This is theoretically possible for two reasons First, the stagnation of blood flow would allow tissues to be exposed to the effects of the contrast media for a longer time period Second the chronically ischemic tissue bed experiences a shift to anerobic metabolism with an increase in glucose consumption lactate production a decrease in pH and ion shifts [11-13] If ischemia is severe enough there may be a release of cardiac lysosomal enzymes[1] which may impair transport functions of cell membranes This would lessen the metabolic differences between intracellular and extracellular spaces The increased total CO produced by ischemia[13] would offer a better buffering capacity than normal tissue at normal rates of blood flow These conditions would favor the kind of changes in P50 seen in our study done in a highly buffered red blood cell solution The magnitude of these effects in vivo is unknown *In this regard* Caulfield and colleagues using a protocol similar to ours found that the effect of Renografin on ionized calcium was of a greater magnitude and duration in patients with coronary artery disease than in normals

When the normal sequence of cardiac angiography was reversed (i e coronary arteriography performed prior to left ventriculography) no effect on P50 was detected one minute or five minutes after the injection of the left coronary artery This suggests that the effects are additive and dose related as seen in our in vitro studies

The ultimate effects of contrast medium on oxyhemoglobin dissociation are complex and dependent upon dosage and blood flow but the direction of change in P50 is probably most influenced by the buffering capacity of the ambient tissue

Summary

The effect of the addition of radiographic contrast material (Renografin) to blood on the oxyhemoglobin dissociation curve and P50 was measured by a metabolic deoxygenation tech

nique in a strongly buffered red cell suspension With incubation time constant increasing doses produced progressive decreases in P50 With incubation time varied at a constant dose a decrease in Po0 was seen after only one minute

In addition in vivo studies were performed on 11 patients undergoing cardiac catheterization Simultaneous proximal coronary sinus and aortic samples were drawn as controls and then at one minute and five minutes after injection of the left coronary artery In eight patients studies were performed after and in three prior to left ventriculography

At one minute after left coronary injection there was a significant decrease of coronary sinus as compared to aortic P50 ($p < 10$) (only when left ventriculography was performed prior to coronary arteriography)

The magnitude of these effects in vivo is unknown but they would be expected to be more severe in areas distal to a critical coronary lesion due to stasis of blood flow and ischemic metabolic changes

REFERENCES

1 Braunwald E and Swan H J C ed Cooperative study on cardiac catheterization Circulation 37(Suppl. 3) 81 1968
2 Lachlan M Biochemical and other changes occurring in infants during angiography Proc R Soc Med. 63 46 19 0
3 Rosenthal A Litwin B S., and Laver M B Effect of contrast media used in angiocardiography on hemoglobin-oxygen equilibrium Invest Radiol 8 191 1973
4 Friesinger G C Schaffer J Criley M Gaertner R A and Ross R S Hemodynamic consequences of the injection of radiopaque material Circulation 31 730 1965
5 Levin A R Grossman H., Schubert E T., Winchester P and Gilladoga A Effect of angiocardiography on fluid and electrolyte balance Am J Roentgenol. 105 777 1969
6. Marshall M and Henderson G A Tendency to acidosis following injection of radio opaque contrast material, Br J Radiol 41 190 1968
7 Berg G R Hutter A M., and Pfister R C Electrocardiographic abnormalities associated with intravenous urography N Eng J Med 289 87 1973
8 Caulfield, J B Zir L., and Harthorne W J Blood calcium levels in the presence of arteriographic contrast material Circulation 52 119 1975
9 Lichtman M A., Murphy M S Whitbeck A A., Pogal, M and Lipchik, E. O Acidification of plasma by the red cell due to radiographic contrast materials, Circulation 52:943 1975
10 Rosenthal, A., and Mesrobian A. The relationship between angiography intraerythrocytic pH and hemoglobin equilibrium Invest Radiol 10 140 1975
11 Cameron B F Biphasic blood oxygen dissociation curves in hemoglobin S hemoglobinopathies. Sickle cell heterozygotes Biochem. Biophys Res Commun. 43 888 1971
12 Longmuir I S and Chow J Rapid method for determining effect of agents on oxyhemoglobin dissociation curves J Appl. Physiol 28 343 1970
13 Naeraa N Strange P E., Bove E and Severinghaus, J W pH and molecular CO components of the Bohr effect in human blood, Scand J Clin. Lab Invest 18 96 1966
14 Scheuer J Myocardial metabolism in cardiac hypoxia, Am J Cardiol. 19 385 1967
15 Brachfeld N Maintenance of cell viability Circulation 39 and 40(Suppl. 4) 207 1969
16 Katz, A.M Effects of interrupted coronary flow upon myocardial metabolism and contractility Progr Cardiovasc Dis. 10 450 1968
17 Brachfeld N and Gemba R Mechanisms of myocardial cell death Release of lysosomal hydrolases after ischemia, Clin Res. 13 524 1965
18 Williamson J R., Schaffer S W., Ford, C., and Safer B Contribution of tissue acidosis to ischemic injury in the perfused rat heart Circulation 53(Suppl. 1) 3 1976
19 Halpern P., Fleishman, R. G., Keupe D., et al. The Bohr effect related to blood and erythrocyte pH Am J Physiol. 205 377 1963

Primary myocardial disease Correlation with clinical findings, angiographic and biopsy diagnosis

Follow up of 139 patients

Earl K Shirey M D
William L Proudfit M D
William A Hawk M D
Cleveland Ohio

It is customary to apply the term primary myocardial disease or cardiomyopathy to an abnormal state of the myocardium unrelated to arterial hypertension coronary atherosclerosis, syphilitic rheumatic and congenital heart disease These terms have been used to denote an affection of unknown etiology and conditions having a specific cause [3] On the basis of ventricular function and pathologic findings Goodwin[4] has classified the cardiomyopathies into four main types congestive hypertrophic with or without obstruction constrictive (restrictive) and obliterative The clinical manifestations of patients with these types of myocardial disease of [illegible]wn or unknown etiology may be similar [3] However a variety of clinical features and hemodynamic measurements may have some correlation with prognosis Hatle and co workers and Goodwin noted a favorable course in patients with cardiac hypertrophy and in others in whom systemic hypertension developed but patients with low voltage (ECG) left atrial enlargement high filling pressure low cardiac output and elevated pulmonary arterial resistance seemed to have unfavorable clinical courses Feild and colleagues found a high survival rate in groups of patients with a mass/volume ratio greater than 0 90 and ejection fraction greater than 0 90 suggesting hypertrophy was an important compensatory mechanism According to Demakis and co workers [3] the long term prognosis of patients with congestive heart failure is related to the time required for the heart to return to normal size following conventional therapy Shugoll and associates[1] found that there was no relationship between the size of the heart and survival

In this study we have attempted to correlate various clinical manifestations of patients with primary myocardial disease compare the course of patients with congestive and noncongestive cardiomyopathies and assess the prognostic value of myocardial biopsy

From the Department of Card logy and the Department of Pathology The Cle eland Clinic Fou d ti n and the C l eland Clin c Educational F undation Clevel nd Oh o

Received fo publication O t 16 19 8

Accepted for publication Jan 3 19 J

Reprint requests Earl K Shirey M D Th Clin Ce te 9500 Fu l d A e Cl eland, Ohio 44106

Materials and methods

One hundred fifty nine patients were selected for this study The criteria for selection were a myocardial biopsy and an angiographic diagnosis of primary myocardial disease There was no evidence of congenital rheumatic syphilitic heart disease or obstruction of the coronary artery circulation greater than 50% The term primary myocardial disease applies to the idiopathic group and those with specific etiology as suggested by Segal and colleagues [3] The biopsy technic was described in 1972 To avoid a possible error in diagnosis 16 patients with systemic blood pressures of 150/100 mm Hg and above were

0002 8 03 80/0 0198 + 10$01 00/0 © 1980 The C V Mosby Co

excluded Although the diastolic blood pressure may be temporarily elevated in patients with primary myocardial disease and congestive failure the findings are similar in hypertensive cardiovascular disease [1, 4, 6] One patient who died one day after a myocardial biopsy was excluded Of the remaining 142 patients three were lost to follow up (97 8% follow up)

Clinical features

The history and physical findings elicited days to several weeks prior to cardiac catheterization and angiographic studies were reviewed A history of congestive heart failure or a cardiac arrhythmia may be inaccurate therefore only abnormal clinical findings present on clinical examination were recorded

The following manifestations were encountered

1 Congestive heart failure—ventricular gallop (third heart sound) rales hepatomegaly or peripheral edema alone or in any combination on physical examination Noncardiac causes of rales hepatomegaly and peripheral edema were excluded

2 Cardiac arrhythmia—an arrhythmia other than sinus arrhythmia present on a standard electrocardiogram

3 Angina pectoris—discomfort in the anterior chest that was precipitated by excessive physical activity or emotional stress or by both relieved within 15 minutes by rest or nitroglycerin Some patients had rest pain

4 Chest wall pain—discomfort usually sharp and unrelated to physical or emotional stress of seconds to hours in duration

5 Shortness of breath—breathlessness of short duration during activity or at rest

6 Palpitation—awareness of a rapid and forceful heartbeat that was usually regular

7 Fatigue—exhaustion or tiredness mostly during activity

Eight patients had drinking patterns considered to be abnormal Five patients drank beer only in quantities of 1 5 to 5 5 quarts daily for five to 15 years The others reported a daily intake of the same beverage in excess of 1½ pints seven to 26 ounces of whiskey or 26 ounces of wine daily for five to 25 years

Coexisting disease Twelve patients had diabetes mellitus Chronic obstructive pulmonary disease was present in one patient The diagnoses were polyneuropathy multiple myeloma hypothyroidism lupus erythematosus and rheumatoid arthritis in five patients (one patient each)

Cardiac catheterization and angiographic diagnosis The diagnosis was based on analysis of pressure curves hemodynamic findings and single plane angiograms (multiple views) The classification of Goodwin was used

1 Congestive—dilatation and generalized impairment of contractility of the left ventricle were present

2 Hypertrophic with or without obstruction—size of the left ventricular cavity was normal or small with accentuated trabecular pattern and prominent papillary muscles with or without functional constriction of septal perforators in systole

3 Constrictive (restrictive)—the left ventricular chamber was dilated or of normal size with impaired contractions or reduced diastolic pulsations or both with an absent atrial kick Most of the hemodynamic findings and the double density parallel to the cardiac border usually demonstrated by selective coronary arteriography in patients with pericardial disease were absent

Myocardial biopsy In most patients a myocardial biopsy was performed a few days following cardiac catheterization and angiographic studies The other patients had biopsies performed two to six weeks later The method for preparing and staining the biopsy specimens has been described

The light microscopic findings

1 Myocardium—no pathologic diagnosis

2 Myocardial hypertrophy—increase in breadth of muscle fibers by enlargement and blunting of the ends of myocardial cell nuclei with and without perinuclear vacuoles or clear zones

3 Myocardial fibrosis—increase in connective tissue surrounding small arteries and arterioles and connective tissue between muscle fibers

4 Cellular infiltration—presence of neutrophils lymphocytes or plasma cells in the interstitium

5 Amyloid deposition—pale pink staining ground glass appearing interstitial deposits (hematoxylin and eosin) appear as magenta colored metachromatic material on crystal violet stained preparation

Table I Clinical manifestations of 139 patients

	No of patients	*Per cent*
Congestive heart failure	54	38 5
Cardiac arrhythmia	40 (total)	28 7 (total)
Supraventricular	18	45 0
Ventricular	21	52 5
Complete heart block	1	2 5
Angina pectoris	28	20 1
Other symptoms	29	20 8
Asymptomatic	8	5 7

14 patients had angina pectoris only
Shortness of breath, palpitations chest wall pain or fatigue only

6 Small vessel disease—walls of the vessels 70 to 150 microns in diameter showed an increase in stainable collagen (Masson stain) beneath the intima and irregularly throughout the muscle layer

7 Basophilic degeneration—deposits of blue gray hyaline material within the myocardium (hematoxylin and eosin) The material stained intensely with PAS stain and failed to give a metachromatic reaction with crystal violet

Management Congestive failure was treated with sodium restriction digitalis preparations and diuretics The duration of bed rest and limited activity depended on the response to medical management The average period of bed rest was four to six weeks Cardiac arrhythmias were managed with the usual antiarrhythmic drugs digitalis preparations quinidine sulfate and procainamide A permanent cardiac pacemaker for conduction defects was inserted in four patients The patients with chest pain suggestive of angina pectoris were advised to avoid precipitating factors Rest pain was treated with mild analgesics The same medication was prescribed for chest wall pain Cerebral embolus or pulmonary embolus occurred in four patients All but one received anticoagulant therapy which was discontinued in one patient because of gastrointestinal bleeding General measures consisted of adequate rest and a well balanced diet Fatigue and alcoholic beverages were to be avoided A vitamin supplement was added when a nutritional factor was suspected The two patients with hypertrophic cardiomyopathy with obstruction received propranolol in a dose of 80 mg daily Patients with polyneuropathy and lupus erythematosus received corticosteroids The same drug was administered to patients with histologic findings of cellular infiltration and to two patients with severe congestive failure and uncontrolled cardiac arrhythmias The patient with hypothyroidism was treated with thyroid medication

Follow up Data on 139 patients were obtained from attending physicians patients spouse or members of the family by questionnaires and by telephone contacts In some patients the information was recorded from the clinical and medical records and autopsy reports From these data it was difficult to determine the duration of clinical heart disease, therefore the follow up period was the interval of time between cardiac catheterization and angiography and the last date examination data was obtained or the death of the patient There were 99 men (mean age 4? years) and 40 women (mean age 43 3 years) The follow up of surviving patients was a minimum of 13 months and a maximum of 11 9 years (14 months) mean 5 4 years (65 months)

Results

Clinical manifestations The clinical findings at the initial examination are listed in Table I Congestive failure was present in 48 of 11 patients (42 4%) with congestive cardiomyopathy Five of eight patients (62 5%) with constrictive cardiomyopathy and one of 18 patients (5 5% with hypertrophic myocardial disease had the same clinical manifestations Of the 54 patients with congestive failure 11 had coexisting cardiac arrhythmias Atrial fibrillation (four patients) and premature ventricular contractions (three patients) were the most common arrhythmias Atrial flutter (two patients) and premature atrial contractions (two patients) were the other arrhythmias

Cardiac arrhythmia without congestive failure was present in 29 patients (20 8%) The most common arrhythmias were premature ventricular contractions and atrial fibrillation These arrhythmias (20 patients) ventricular tachycardia (two patients) and supraventricular tachycardia (one patient) occurred in those with congestive cardiomyopathy Both premature ventricular contractions and ventricular tachycardia occurred in two patients ventricular tachycardia and ventricular fibrillation were present in one other patient Premature ventricular contractions was the only arrhythmia in one patient with constrictive cardiomyopathy Complete heart

block and ventricular tachycardia were the manifestations in two patients with hypertrophic myocardial disease.

Chest pain suggestive of angina pectoris was elicited in 28 patients (20.1%). One of these had atypical angina (chest discomfort relieved by rest in 30 minutes). Angina pectoris was the only symptom in 19 of 28 patients. In these the angiographic diagnosis was congestive cardiomyopathy (15 patients) and hypertrophic cardiomyopathy (four patients).

Of 29 patients (20.8%) with shortness of breath, palpitations, chest wall pain, or fatigue only, 20 had congestive myopathy. The others had hypertrophic (seven patients) and constrictive cardiomyopathy (two patients).

Only eight patients (5.7%) had no symptoms. The electrocardiographic findings shown in Table II were the reasons for the investigations. In three patients a systolic murmur was present. The types of myopathy were congestive (four patients) and hypertrophic without obstruction (four patients).

Cardiac catheterization and angiographic findings. The diagnosis of congestive cardiomyopathy was made in 113 patients. Prolapse of the mitral valve without mitral regurgitation was noted in two patients. One of 11 patients with mitral regurgitation had prolapse of the mitral valve. In 18 patients the findings were consistent with hypertrophic cardiomyopathy. Two of these 18 patients had evidence of left ventricular outflow tract obstructions without mitral regurgitation. Constrictive cardiomyopathy was the diagnosis in eight patients.

Myocardial biopsy. The biopsy played a minor role in the management in most patients, but it provided an opportunity to compare tissue diagnosis with other parameters. Myocardial hypertrophy or fibrosis or both was present in 43 of 54 patients (79.6%) with congestive failure. The same tissue diagnosis was made in six of the eight asymptomatic patients (76%) and in 46 of 77 symptomatic patients (58%) without congestive failure. Seventy-four of 113 patients (65.4%) with congestive cardiomyopathy had the same biopsy findings as did 16 of 18 patients (88.8%) and five of eight patients (62.5%) with hypertrophic and constrictive myopathy, respectively. Small vessel disease was not associated with specific clinical manifestations (no angina pectoris). It was present in two of eight patients (25%) with constrictive myopathy compared to two of 18 (11%) and two of 113 patients (1.8%) with hypertrophic and congestive cardiomyopathy, respectively. Shortness of breath, palpitation, chest wall pain, or fatigue were the most frequent symptoms and congestive myopathy was present in most of the 35 patients (94%) with no pathologic diagnosis.

Table II. Indications for study in asymptomatic patients

	Type of cardiomyopathy	
	No. of patients	
Abnormal findings	*Congestive*	*Hypertrophic*
ECG changes		
LBBB	3	
RBBB		1
Infarction†	1	1
LVH		2

LBBB = left bundle branch block; RBBB = right bundle branch block; LVH = left ventricular hypertrophy.
Cardiac catheterization and angiographic diagnosis.
†Inferolateral (QRS abnormalities) and intramural.

Mortality rate. The 8 year total mortality rate was 37.4% (52 of 139 patients). Although some of the information obtained concerning the mechanism of death may not be reliable, myocardial disease was the most likely cause in 47 of the 52 patients (cardiac mortality rate 33.8%). Cerebral vascular accident (cerebral embolism not absolutely excluded), drug overdose, self-inflicted gunshot wound, and possible pulmonary embolus following pelvic surgery were considered noncardiac deaths in five patients. The minimum and maximum survival for 47 patients whose deaths were considered cardiac was two weeks and 90 months, respectively; mean 2.1 years (25.2 months). Thirty-five deaths were considered to be caused by congestive failure. In five of these the initial findings were chest pain, shortness of breath, palpitations, or cardiac arrhythmia. A cardiac arrhythmia was the most likely cause of death in 12. Arrhythmia was suspected in ten of 11 deaths in patients without congestive failure or cardiac arrhythmias or both in the past (including one asymptomatic patient). There were four sudden deaths: two patients were found dead in bed, one collapsed in a department store, and one died while running.

The survival curves shown in Fig. 1 using the life table method (Table III) demonstrate a

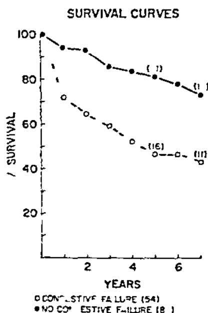


Fig. 1. Survival curve for patients with and without congestive heart failure. *The number of patients living at the beginning interval in parenthesis.*

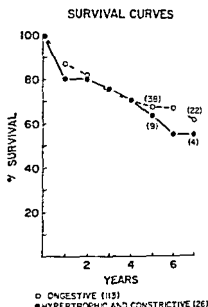


Fig. 2. Survival curve for patients with congestive cardiomyopathy; the hypertrophic and constrictive types are compared. *Number of patients in parenthesis.*

Table III. Life table

Interval followed (T)	No. of patients: Last report: Dead	No. of patients: Last report: Living*	No. of patients: Total no. persons living at beginning of interval
0-1	15 (5)	(1)	54 (85)
1-2	4 (1)	3 (1)	39 (79)
2-3	4 (6)	1 (10)	32 (77)
3-4	3 (1)	3 (20)	27 (62)
4-5	[illegible] (1)	3 (9)	21 (41)
5-6	0 (1)	(12)	16 (31)
6-7	1 (1)	1 (1)	13 (18)
7+	1 (1)	10 (14)	11 (15)

First [illegible] failure, others in parentheses.
*[illegible] interval or dead from intercurrent disease.

significant difference in survival rates in one year ($P < 0.001$) and five years ($P = 0.001$) in patients with and without congestive heart failure. The survival curves were based on the methods described by Cutler and Ederer. The chi square method with Yates' correction formula was used to determine the statistical significance of different mortality rates. In 54 patients with congestive failure, the 5 year total mortality rate was 57.4%. There were three noncardiac deaths resulting in a five year cardiac mortality rate of 51.8%. The highest cardiac mortality rate was in the first year (27.7%). Four of 15 patients (26.6%) with congestive failure who died within one year had a coexisting cardiac arrhythmia (Table IV). The next highest number of cardiac deaths occurred between one and three years (eight patients). Of these, two patients (25%) had congestive failure and a cardiac arrhythmia. The 5 year cardiac mortality rate of 85 patients without congestive failure was 16.4% (only one noncardiac death). Of these, the highest cardiac mortality rate occurred in 29 patients (34.4%) with a history of shortness of breath, palpitation, chest wall pain, or fatigue. The groups with the least 5 year mortality rate were asymptomatic (12.5%), angina pectoris only (10.5%), and cardiac arrhythmias only (3.4%).

Of the 12 patients who had diabetes mellitus, seven (58%) had congestive heart failure or cardiac arrhythmias or both. There were six cardiac deaths (50%). Three of these patients had congestive failure or cardiac arrhythmias or both. Congestive heart failure was the cause of death in the one patient with hypothyroidism. The four patients with polyneuropathy, multiple myeloma, rheumatoid arthritis, or lupus erythematosus had been followed for a minimum of 40 months.

The survival curves of patients with congestive cardiomyopathy and combined hypertrophy and

Table IV Relation of clinical manifestations and mortality

Presenting clinical symptom	Total no of patients	Mortality: Years after cardiac catheterization 0-1	1-2	2-3	3-4	4-5	5-6	6-7	7+	Cardiac mortality (per cent)	Total mortality (per cent)
Congestive failure	43	11	3 (3)	3	3	2		1	1	24 (55 8)	27 (6[illegible])
Congestive failure and arrhythmias	11	4	1	1						6 (54 5)	
Arrhythmias without failure	29	(1)			1			1	1	3 (10 3)	4 (13 [illegible])
Angina pectoris only	19	1	1							2 (10 5)	
Other symptoms	29	4		5		1	1		(1)	11 (37 9)	12 (41 3)
Asymptomatic	8			1						1 (12 5)	
Total	139									47 (33 8)	52 (37 4)

Non cardiac deaths in parentheses

Other symptoms—dyspnea palpitation chest wall pain or fatigue

constrictive cardiomyopathy are demonstrated in Fig 2 The death rate of three patients with amyloid heart disease accounts for the high mortality rate of the noncongestive myopathy group within the first year The average annual mortality rate in the first five years for patients with congestive myopathy was 6 5% per year the average annual attrition rate for patients with hypertrophic and constrictive myopathy was 7.2% per year If the three patients with amyloid heart disease (constrictive type) are excluded the average attrition rate for the first five years for the combined types (hypertrophic and restrictive) was 5 9% annually

Patients whose biopsies showed no pathologic diagnosis survived the longest (Fig 3) Excluding the patients with amyloid heart disease myocardial fibrosis with or without hypertrophy only was associated with the highest mortality rate (Table V) When 18 patients with myocardial hypertrophy or fibrosis or both and cellular infiltrate small vessel disease or basophilic degeneration are included the death rate was similar (46 6%) In contrast the death rate was 16 6% in six patients with cellular infiltrate small vessel disease or basophilic degeneration only Nineteen patients were examined at autopsy Biopsy and autopsy histologic findings in all patients are compared in Table VI The same tissue diagnosis was present in almost one half of the patients (47 4%) In four of ten patients with a new diagnosis the autopsy findings were absent in the biopsy and in six patients not all of the pathologic changes were present in the two groups

Discussion

It is difficult to determine the accuracy of the history (including drinking habits) to monitor how carefully treatment was followed or to control all the factors that could influence the course of the patient with primary myocardial disease For example only eight of 139 patients (5 8%) admitted the heavy use of alcohol which is more than 50% below the general adult population studied by Cahalan and colleagues[1] Although abstinence was adviced the degree of compliance is unknown The same applies to rest and limitation of physical activity and emotional stress The selection of medications and dosage of drugs could affect survival The dose of propranolol (80 mg daily) in the two patients with hypertrophic cardiomyopathy with obstruction could have been ineffective (50% mortality rate) The number of patients is too small to be significant but a recent report by Frank and associates[1] suggested high doses (average 340 mg daily) may be associated with a favorable prognosis Hardarson and co workers[14] found beta adrenergic blocking agents in a dose range of 20 to 240 mg daily to be disappointing but concluded a higher dosage may offer better protection from sudden death If the limited value of history variations in ability and experience of physicians attending the patient and inability to measure cooperation of the patient are accepted the correlation of various parameters with survival may be meaningful.

Congestive heart failure was associated with a high mortality rate (56%) The addition of a

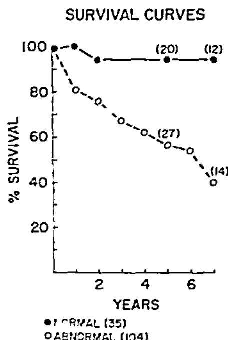


Fig 3 Survival curves for patients with normal and abnormal microscopic findings (myocardial biopsy) *Number of patients in parenthesis*

Table V Correlation of biopsy diagnosis with cardiac mortality

	Total no of patients	*Cardiac deaths (per cent)*
Myocardium, no pathologic Dx	35	5.7
Myocardial hypertrophy	20	30.0
Myocardial fibrosis	21	52.3
Myocardial hypertrophy and fibrosis	[illegible]6	50.0
Cellular infiltrate	3	33.3
Amyloid	3	100.0
Small vessel disease	1	0
Basophilic degeneration	2	0
Myocardial hypertrophy and/or fibrosis with CI, SVD, or BAS	18	33.3

Abbreviation CI = cellular infiltrate SVD = small vessel disease BAS = basophilic degeneration

cardiac arrhythmia seemed to have no major influence on prognosis (mortality rate 54.5% however the frequency or duration of arrhythmias was not determined in this group nor in the patients with arrhythmias only Ambulatory electrocardiographic monitoring was not performed routinely in all patients in search of an arrhythmia therefore total information could be limited Patients with shortness of breath palpitations chest wall pain and fatigue had a mortality rate of 38% Perhaps the history was inaccurate or arrhythmias or congestive failure were undetected, but the findings suggest these symptoms cannot be predictive of a good prognosis In contrast those without symptoms angina pectoris only and arrhythmias only had a favorable course

Table VI Comparison of biopsy and autopsy findings in 19 patients

Tissue diagnosis	*No of patients (%)*		*Time interval in months (mean)*
Same diagnosis	9	(47.4)	0.5-90 ([illegible]0.5)
New diagnosis (biopsy or autopsy)	10	(52.6)	[illegible] 8 ([illegible])

The influence of alcohol on eight patients is difficult to determine There were no distinctive physical findings however in two patients there were questionable cloven and spinous T wave deformities CR leads suggested by Evans were not recorded. Congestive heart failure was common (50%) The incidence was slightly lower in the nonalcoholic group (38%) but the cardiac mortality rate was similar in both groups (37.5% and 33.5% respectively) Others have reported that the groups cannot be separated by the mortality rates[11] In patients with alcoholic cardiomyopathy congestive failure was reported by Tobin and co workers[1] in 31 of 39 patients (79.4%) and in all of the 48 patients evaluated by McDonald and associates[2] because it was the criterion for admission to the study the cardiac mortality rate in these two reports was 25.6% and 39.5% respectively not unlike our experience The histologic appearance of biopsy specimens failed to distinguish between the groups Except for the groups having no small vessel disease or no pathologic diagnosis the same changes have been demonstrated by others[1-3] The identical morphologic changes of biopsy and postmortem specimens of myocardium in a single patient who admitted to an excessive use of alcohol are similar to the experience reported by Szanto and Meister

Histologic findings have rarely provided a cause for myocardial disease and it has been disap-

pointing in determining the management. The clinical course and survival depend on many factors and to be sure it is difficult to relate to a myocardial biopsy, but several observations from the study are of interest. Myocardial hypertrophy may not favorably influence prognosis. This is suggested by a cardiac mortality rate almost five times higher in the group with hypertrophy (biopsy, ECG or both) and no fibrosis. Electrocardiographic evidence of hypertrophy (left ventricular hypertrophy) was present when there was ST segment depression in Leads V_5 and V_6, diphasic or inverted T waves, and delayed intrinsicoid deflections (0.05 sec or more). Electrocardiograms were recorded on high fidelity photographic machines (Sanborn Twin Beam). This is contrary to observations made by other investigators. The different results could be explained by methods used for recognizing hypertrophy (ECG and angiograms), degree of cavity dilatation or hypertrophy or both, and congestive heart failure. In 18 patients with congestive failure the mortality rate was 50% in the groups with and without hypertrophy and no fibrosis (patients with amyloid excluded). Another possibility is the presence of biochemical defects in the hypertrophic heart that are considered to contribute to reduced contractility. As expected, hypertrophy (biopsy or ECG or both) and fibrosis and fibrosis without hypertrophy was associated with a high mortality rate (52% and 36%, respectively).

The role of small arteries of the heart as the cause of various clinical syndromes has interested many investigators. James and Fish have studied extensively the small arteries (100 to 1,000 microns) in humans and concluded that widespread involvement could be a cause of idiopathic cardiomyopathies. Evaluation of the anatomic features and the clinical events has suggested that narrowing of multiple small arteries could cause chest pain that resembles angina pectoris, arrhythmias, and conduction disturbances (syncope and sudden death) and generalized cardiac enlargement with and without congestive heart failure. In 1974 Kannel and co-workers suspected small vessel disease as the cause of congestive heart failure in a group of diabetic patients in the Framingham study. In the same year Hamby and associates found subendothelial proliferation and fibrosis in small coronary arteries in a similar group of patients and incriminated these changes as an etiologic factor in heart disease. Small vessel disease has been considered to be a possible cause of many of the features of the mitral valve prolapse syndrome. It seems difficult to derive from biopsies the prevalence and significance of small vessel disease. The one or two specimens (closed chest technic) of the septum or ventricular wall are of limited value in patients with focal lesions and do not permit evaluation of sinus node or atrioventricular node arteries. Small vessel disease shown in biopsy studies (patients with amyloid excluded) in six of 139 patients (4.3%) and in one of 19 patients at autopsy (5.3%) would suggest that an anatomic abnormality of the small arteries is infrequent. Only one or two vessels in the biopsy specimens were affected. Because the clinical events were ventricular arrhythmias (two patients), chest wall pain (two patients), shortness of breath (one patient), and no symptoms (one patient), the findings probably excluded a generalized or diffuse process and played a minor role. Narrowing of small coronary coronary arteries in two of four patients with sudden death could be significant but difficult to prove. The meaning of multiple intravascular thrombi of small arteries (postmortem) in the single patient with congestive failure is unknown. The absence of structural changes in the microcirculation of 12 patients with diabetes mellitus (two autopsies) does not correspond with other observations. On the other hand, James recognized normal small arteries in some diabetic subjects and had difficulty in providing an explanation. Angina pectoris in 28 patients without small vessel disease and the absence of this clinical syndrome in six patients with small coronary artery disease is noteworthy.

Myocardium with no pathological diagnosis in 35 of 139 patients (25%) probably means that focal changes were missed by the biopsy technic. Although a negative biopsy does not absolutely exclude myocardial disease, it was associated with a low cardiac mortality rate. The survival curve remains flat after two years. The decreased incidence of congestive failure (17%) and cardiac mortality rate (17%) compared to those with abnormal biopsies (46 and 60%, *respectively*) would suggest that patchy histologic changes are present and possibly predictive of an improved

prognosis A comparison of the biopsy and autopsy histological material revealed the same findings in less than one half of the 19 patients The average interval of time between the biopsy and autopsy examination was similar in the two groups Consequently the patchy distribution of various histologic changes known to be present in cardiomyopathies provides the best explanation for the variable findings in some patients In two patients only, the biopsy diagnosis was myocardium with no pathologic diagnosis and on post mortem examination 13 and 31 months post biopsy there was hypertrophy and hypertrophy and fibrosis respectively In the other eight patients with a new diagnosis myocardial hypertrophy or fibrosis or both were present in the biopsy and autopsy specimens Because these findings were associated with a high mortality rate the differences in the biopsy and autopsy diagnosis would not seem to be important

Summary

The purpose of this study was determination of the prognostic value of clinical and tissue (biopsy) findings of 139 patients with cardiomyopathy The types of cardiomyopathy were congestive (113 patients) and hypertrophic or constrictive (26 patients) The mean follow up period of all patients was 4.3 years Follow up of the survivors was between 13 months and 11.9 years mean 5 4 years Of the 47 cardiac deaths (33 8%) the minimum and maximum follow up was two weeks and 7 5 years respectively (mean 2 1 years) atients with congestive heart failure had the ighest five year cardiac mortality rate (51.8%) Coexisting cardiac arrhythmia had no influence on prognosis and an arrhythmia only was benign in most patients Myocardial hypertrophy or fibrosis or both and myocardium with no pathologic diagnosis had prognostic value Small vessel disease was infrequent and not associated with specific clinical manifestations

REFERENCES

1 Fowler N O and Gueron M Primary myocardial disease Circulation 32 830 1965
2 Mattingly T W The clinical concept of primary myocardial disease A classification and a few notes on management and prognosis Circulation 32 845 1965
3 Segal, J P., Harvey W P and Gorel T Diagnosis and treatment of primary myocardial disease Circulation 32 837 1965
4 Goodwin J F Clarification of the cardiomyopathies Mod Concepts Cardiovasc Dis 41 41 1972
5 Goodwin J F Congestive and hypertrophic cardiomyopathies Lancet 1 731 1970
6 Hatle L. Orjavik O., and Storstein O Chronic myocardial disease I Clinical picture related to long term prognosis Acta Med Scand 199 399 1976
7 Goodwin J F Hypertrophic disease of the myocardium Progr Cardiovasc Dis 16 199 1973
8 Hatle L., Stake G and Storstein O Chronic myocardial disease II Haemodynamic findings related to long term prognosis Acta Med. Scand 199 407 1976
9 Feild B J., Baxley W A., Russel R O Jr Hood W P Jr., Holt J H., Dowling J T and Rackley C E Left ventricular function and hypertrophy in cardiomyopathy with depressed ejection fraction Circulation 47 1022 1973
10 Demakis J G., and Rahimtoola S H. Peripartum cardiomyopathy Circulation 44 964 1971
11 Shugoll G I., Bowen P J Moore J P., and Lenkin, M. L Follow up observations and prognosis in primary myocardial disease Arch. Intern Med 129 67 1972
12 Shirey E K Hawk W A Mukerji, D and Effler D B Percutaneous myocardial biopsy of the left ventricle Experience in 198 patients Circulation 46 112 1972
13 Cutler S J., and Ederer F Maximum utilization of the life table method in analyzing survival, J Chron Dis. 8 699 1958
14 Cahalan D., Cisin I H., and Crossley H M American drinking practices a national study of drinking behavior and attitudes New Brunswick N.J., 1969 Rutgers Center of Alcohol Studies Monograph No 6
15 Frank, M J Abdulla A. M., and Canedo M. I Long term medical management of hypertrophic obstructive cardiomyopathy (Abstr) Am J Cardiol. 39 271 1977
16 Hardarson T., De La Calzada C S Curiel, R and Goodwin J F Prognosis and mortality of hypertrophic obstructive cardiomyopathy Lancet 1 482 1973
17 Evans W Electrocardiograms of alcoholic cardiomyopathy Br Heart J 21 445 1959
18 Evans W Alcoholic cardiomyopathy AM HEART J 61 556 1961
19 Tobin J R Driscoll J F Lim M T., Sutton G C Szanto P B and Gunnar R M Primary myocardial disease and alcoholism The clinical manifestations and course of the disease in a selected population of patients observed for three or more years Circulation 35 754 1967
20 McDonald C D., Burch G E and Walsh, J J Alcoholic cardiomyopathy managed with prolonged rest. Ann Intern Med. 71 681 1971
21 Bollinger Prof Ueber die haufigkeit and ursachen der idiopathischen herzhypertrophic in Munchen Deutsche Med Wchnschr 10 180 1884
22 Aufrecht Dr Die alkoholische Myocarditis mit nachfolgender lebererkrankung und zietweiliger Albuminurie Deutsche Arch. Klin Med 54 615 1895
23 Batsakis J G Pathology of the heart and blood vessels, ed. 3 Springfield Ill Charles C Thomas, Publisher 479 pp 1968
24 Szanto P B and Meister H. P Alcoholic myocardiopathy (Abstr) Am J Clin Pathol. 39 294 1963
25 Olson R E The contractile proteins of heart muscle Am J Med. 30 692 1961
26 Katz A M Biochemical defect in the hypertrophied and failing heart—deleterious or compensatory? Circulation 47 1076 1973
27 James T N Observations on the cardiovascular involvement including the cardiac conduction system, in progressive muscular dystrophy AM HEART J 63 4 1962

28 Richardson H L Graupner K I and Richardson M E. Intramyocardial lesions in patients dying suddenly and unexpectedly J A M A 195 254 1966
29 Likoff W., Segal B L and Kasparian H Paradox of normal selective coronary arteriograms in patients considered to have unmistakable coronary heart disease N Engl J Med 276 1063 1967
30 Barath J., Veres, J and Csorgey M The role of functional factors and special vascular sphincter apparatuses in myocardial infarction Acta Med Acad Sci Hung 22 111 1966
31 James T N An etiologic concept concerning the obscure myocardiopathies Progr Cardiovasc Dis 7 43 1964
32 James T N and Fish C Observations on the cardiovascular involvement in Friedreich s ataxia AM HEART J 66 164 1963
33 James T N Frame B and Schatz I J Pathology of the cardiac conduction system in Marfan s syndrome Arch Intern Med 114 339 1964
34 James, T N Small arteries of the heart The George E Brown Memorial Lecture Circulation 56 2 1977
35 Kannel W B., Hjortland M., and Castelli, W P Role of diabetes in congestive heart failure the Framingham Study Am J Cardiol 34 29 1974
36 Hamby R I Zoneraich S., and Sherman L. Diabetic cardiomyopathy J A M A 229 1749 1974
37 Popp R. L. and Winkle R A. Mitral valve prolapse syndrome J.A M.A 236 867 19 6
38 Blumenthal, H T Alex M., and Goldenberg S A study of lesions of the intramural coronary artery branches in diabetes mellitus Arch Pathol 70 13 1960
39 James T N The coronary arteries, J.A M.A 239 1302 1978

prognosis A comparison of the biopsy and autopsy histological material revealed the same findings in less than one half of the 19 patients The average interval of time between the biopsy and autopsy examination was similar in the two groups Consequently the patchy distribution of various histologic changes known to be present in cardiomyopathies provides the best explanation for the variable findings in some patients In two patients only the biopsy diagnosis was myocardium with no pathologic diagnosis and on postmortem examination 13 and 31 months post biopsy there was hypertrophy and hypertrophy and fibrosis respectively In the other eight patients with a new diagnosis myocardial hypertrophy or fibrosis or both were present in the biopsy and autopsy specimens Because these findings were associated with a high mortality rate the differences in the biopsy and autopsy diagnosis would not seem to be important

Summary

The purpose of this study was determination of the prognostic value of clinical and tissue (biopsy) findings of 139 patients with cardiomyopathy The types of cardiomyopathy were congestive (113 patients) and hypertrophic or constrictive (26 patients) The mean follow up period of all patients was 4 3 years Follow up of the survivors was between 13 months and 11 9 years mean 5 4 years Of the 47 cardiac deaths (33 8%) the minimum and maximum follow up was two weeks and 7 5 years respectively (mean 2 1 years) Patients with congestive heart failure had the highest five year cardiac mortality rate (51 8%) Coexisting cardiac arrhythmia had no influence on prognosis and an arrhythmia only was benign in most patients Myocardial hypertrophy or fibrosis or both and myocardium with no pathologic diagnosis had prognostic value Small vessel disease was infrequent and not associated with specific clinical manifestations

REFERENCES

1 Fowler N O and Gueron M Primary myocardial disease Circulation 32 830 1965
2 Mattingly T W The clinical concept of primary myocardial disease A classification and a few notes on management and prognosis Circulation 32 845 1965
3 Segal J P Harvey W P and Gurel T Diagnosis and treatment of primary myocardial disease Circulation 32 837 1965
4 Goodwin J F Clarification of the cardiomyopathies Mod Concepts Cardiovasc Dis 41 41 19?2
5 Goodwin J F Congestive and hypertrophic cardiomyopathies Lancet 1 731 19?0
6 Hatle L Orjavik O and Storstein O Chronic myocardial disease I Clinical picture related to long term prognosis Acta Med Scand 199 399 1976
7 Goodwin J F Hypertrophic disease of the myocardium Progr Cardiovasc Dis 16 199 1973
8 Hatle L Stake G and Storstein O Chronic myocardial disease II Haemodynamic findings related to long term prognosis Acta Med Scand 199 407 1976
9 Feild B J Baxley W A Russel R O Jr Hood W P Jr Holt, J H., Dowling J T and Rackley C E Left ventricular function and hypertrophy in cardiomyopathy with depressed ejection fraction Circulation 47 1022 1973
10 Demakis J G and Rahimtoola S H Peripartum cardiomyopathy Circulation 44 964 1971
11 Shugoll G I Bowen P J Moore J P and Lenkin, M L Follow up observations and prognosis in primary myocardial disease Arch Intern Med 129 6? 19?
12 Shirey E K Hawk W A Mukerji D and Effler D B Percutaneous myocardial biopsy of the left ventricle Experience in 198 patients Circulation 46 11? 19?
13 Cutler S J., and Ederer F Maximum utilization of the life table method in analyzing survival J Chron Dis 8 699 1958
14 Cahalan D Cisin I H and Crossley H M American drinking practices a national study of drinking behavior and attitudes New Brunswick NJ 1969 P? Center of Alcohol Studies Monograph No 6
15 Frank M J Abdulla A M and Canedo M I Long term medical management of hypertrophic obstructive cardiomyopathy (Abstr) Am J Cardiol 39 ?1 197?
16 Hardarson T., De La Calzada C S Curiel R a Goodwin J F Prognosis and mortality of hypertrophic obstructive cardiomyopathy Lancet 1 46? 1973.
17 Evans W Electrocardiograms of alcoholic cardiomyopathy Br Heart J 21 445 1959
18 Evans, W Alcoholic cardiomyopathy AM HEART 61 556 1961
19 Tobin J R Driscoll J F Lim M T Sutton G C Szanto P B., and Gunnar R M Primary myocardial disease and alcoholism The clinical manifestations a course of the disease in a selected population of patients observed for three or more years Circulation 35 ? 1967
20 McDonald C D Burch G E and Walsh, J J Alcoholic cardiomyopathy managed with prolonged re Ann Intern Med 71 681 1971
21 Bollinger Prof Ueber die haufigkeit and ursachen d idiopathischen herzhypertrophie in Munchen Deutsc Med Wchnschr 10 180 1884
22 Aufrecht Dr Die alkoholische Myocarditis mit nachf gender lebererkrankung und zietweilger Albuminur Deutsche Arch Klin Med 54 615 1895
23 Batsakis J G Pathology of the heart and blood vesse ed 3 Springfield Ill Charles C Thomas, Publisher 4 pp 1968
24 Szanto P B and Meister H P Alcoholic myocardi athy (Abstr) Am J Clin Pathol 39 ?94 1963
25 Olson R E The contractile proteins of heart musc Am J Med. 30 692 1961
26 Katz A M Biochemical "defect in the hypertrophi and failing heart—deleterious or compensatory? Circulation 47 1076 19?3
27 James T N Observations on the cardiovascul involvement including the cardiac conduction system progressive muscular dystrophy AM HEART J 63 19?2

28 Richardson H L., Graupner K I and Richardson M E Intramyocardial lesions in patients dying suddenly and unexpectedly J A M A 195 254 1966
29 Likoff W Segal B L. and Kasparian H Paradox of *normal selective coronary arteriograms in patients* considered to have unmistakable coronary heart disease N Engl J Med. 276 1063 1967
30 Barath J Veres, I and Csorgev M The role of functional factors and special vascular sphincter apparatuses in myocardial infarction Acta Med Acad Sci. Hung 22 111 1966
31 James T N An etiologic concept concerning the obscure myocardiopathies Progr Cardiovasc Dis 7 43 1964
32 James T N and Fish C Observations on the cardiovascular involvement in Friedreich s ataxia AM HEART J 66 164 1963
33 James, T N., Frame B and Schatz, I J Pathology of the cardiac conduction system in Marfan s syndrome Arch Intern Med 114 339 1964
34 James, T N Small arteries of the heart The George E Brown Memorial Lecture Circulation 56 2 1977
35 Kannel W B Hjortland M and Castelli W P Role of diabetes in congestive heart failure the Framingham Study Am J Cardiol 34 29 1974
36 Hamby R. I Zoneraich, S., and Sherman L. Diabetic cardiomyopathy J.A M.A *229 1749 1974*
37 Popp R L., and Winkle R A Mitral valve prolapse syndrome J.A M A 236 867 1976
38 Blumenthal H T., Alex M., and Goldenberg S A study of lesions of the intramural coronary artery branches in diabetes mellitus Arch Pathol 70 13 1960
39 James T N The coronary arteries, J.A.M.A 239 1302 1978

Effects of vasodilators on pulmonary hemodynamics and gas exchange in left ventricular failure

Gordon Pierpont, M D Ph D
Kathryn A Hale M D
Joseph A Franciosa M D
Jay N Cohn M D
With the technical assistance of
Susan Ziesche R N
and Mary Wilen
Minneapolis Minn

Sodium nitroprusside is a potent vasodilator that has been widely used to treat hypertensive crises and congestive heart failure and to produce controlled hypotension during surgery Previous studies have demonstrated reduced arterial oxygen tension when nitroprusside is infused to produce controlled hypotension during surgery and when it is given to patients maintained on assisted respiration immediately following coronary artery surgery This hypoxemic effect may also occur in patients with congestive heart failure despite concomitant reduction in pulmonary capillary pressure

Several non parenteral vasodilators including hydralazine and nitrates have also been used in congestive heart failure but their effects on arterial oxygen tension have not been studied Nitrates have a prominent venodilator effect whereas hydralazine dilates primarily arteries Combining these two agents results in hemodynamic effects similar to those of nitroprusside an arterial and venous dilator The present study was designed to further elucidate the mechanisms of nitroprusside induced hypoxemia by measuring blood gases lung mechanics and cardiopulmonary hemodynamics in patients with congestive heart failure In addition the effects of hydralazine and hydralazine combined with isosorbide dinitrate were similarly evaluated not only to determine their effects on arterial oxygen tension but also to correlate changes in oxygenation with the various hemodynamic responses produced

Fr m the Card ascular Di isi n Un ersit f Minnesot Medi al School and th C rd scul and Pulm nary Sect ns V ter n Administrati n H sp tal Mi ne p li Minn

This w rk was upport d part b resea h g n HL 19013 f m th Nati n l Heart and Lung Instit t

Rec   ed for publ ation N   8

Accepted for publicati n De   21   4 r

Reprint request   Joseph A Fran   sa M D V   r   A   t a m Med cal Center M nneapolis Minn 5 41

Methods

Ten male patients with clinical and radiographic evidence of left ventricular failure were selected for study In six of the patients the left ventricular failure was due to ischemic heart disease and in the other four to primary cardiomyopathy All patients were functional Class III or IV (New York Heart Association criteria) while on standard treatment with digitalis and diuretics Their ages ranged from 39 to 79 years with a mean age of 58 years Patients with valvular heart disease (other than functional mitral insufficiency) severe primary pulmonary disease (defined a resting arterial PO < 50 mm Hg or PCO > 50 mm Hg) or patients in shock were excluded from the study

On the day of study all diuretics and vasodilators were withheld so that a relatively steady state existed prior to the administration of test drugs Patients receiving maintenance digitalis therapy or oral antiarrhythmic agents were given their daily doses of these drugs

0002 8 03 80/020208 + 09$00 30/0 © 1980 The C V Mosby Co

Mean pulmonary artery wedge pressure (mm Hg)					*Cardiac index (L/min./M)*				
C	NP	RC	H	H+N	C	NP	RC	H	H+N
31	19	31	24	20	2.2	2.3	2.2	2.⁻	3.1
°8	10	31	25	10	3.2	3.4	2.8	2.8	3.⁻
2	°4	28	31	26	1.8	2.4	1.8	2.1	2.3
°3	18	30	19	16	1.9	2.1	1.⁻	2.5	2.5
°5	11	2_	19	8	2.1	3.4	2.6	5.5	4.-
15	9	14	14	8	2.0	2.1	2.0	2.8	2.5
35	°1	33	38	40	1.3	1.8	1.4	°.1	_3
3⁻	24	30	31	23	2.4	3.5	2.4	2.⁻	3.⁻
_8	21	26	24	18	2.⁻	4.3	2_	3.8	3.⁻
°0	12	24	24	20	1.9	3.0	2.1	3.0	2.8
°6.9	16.⁻	°6.9	24.9	18.9	2.13	2.81	2.10	2.99	3.14
2.1	1.9	1.8	2.2	3.1	0.16	0.26	0.14	0.3_	0.2⁻
	< 001		NS	< 01		< 01		< 01	< 001

Arterial pH					*Calculated arterial oxygen saturation (%)*					*Measured arterial oxygen content (volumes %)*				
C	NP	RC	H	H+N	C	NP	RC	H	H+N	C	NP	RC	H	H+N
⁻.4	⁻.42	7.4°	⁻.53	7.56	96	96	°6	9⁻	°6	—	—	—	—	—
.4⁻	⁻.49	⁻.4⁻	7.4⁻	7.46	96	94	94	°6	91	—	—	—	—	—
7.4	⁻.51	⁻.53	7.4°	⁻.49	9⁻	96	9⁻	96	°6	13.6	12.⁻	13.5	13.0	12.5
.49	⁻.40	.45	7.5°	⁻.52	96	89	96	9⁻	95	14.3	13.2	—	—	—
.44	7.41	.40	⁻.59	7.49	°6	95	96	9⁻	96	16.3	15.⁻	16.5	16.5	15.5
.43	7.43	⁻.41	.42	.41	9⁻	92	°6	9⁻	°5	16.3	15.⁻	16.0	15.8	15.4
⁻.44	.46	7.4⁻	.54	.55	°5	94	9⁻	96	95	13.⁻	13.0	13.6	14.5	13.9
⁻.5°	7.53	7.54	.53	⁻.54	97	95	9⁻	9⁻	9⁻	16.9	15.6	16.5	16.6	16_
⁻.4°	.4_	⁻.4°	.42	7.4⁻	86	71	81	⁻8	88	15.0	12.1	13.9	13.9	16.4
⁻.59	⁻.56	⁻.54	.6	.59	9⁻	95	9°	9⁻	°6	13.8	12.⁻	14._	13.8	13.3
.469	.463	⁻.466	.49°	.50⁻	95.1	91.6	94.6	94.⁻	94.⁻	15.0	13.8	14.9	14.9	14.⁻
.01⁻	.018	.018	.016	.01⁻	1.0	2.4	1.5	1.9	0.9	0.4⁻	0.59	0.5_	0.54	0.5⁻
	NS		NS	< 05		< 05		NS	NS		< 05		NS	NS

$$Q/Q = \frac{Cc\,O - CaO}{Cc\,O - C\bar{v}O}$$

where Cc O = O content of pulmonary capillary blood obtained from the arterial pH and the calculated P O

CaO = systemic arterial O content

C$\bar{v}$O = O content of mixed venous blood where the O contents were calculated from the product of hemoglobin per cent oxygen saturation and 1.34

The ratio of dead space to tidal volume (V_D/V_T) was calculated by

$$V_D/V_T = \frac{P_aCO - P_ECO}{P\,CO}$$

where P_ECO = PCO of expired air

Oxygen delivery index (O DI in c c /min /M) was calculated as the product of cardiac index and arterial oxygen content

Statistical analysis was performed using Stu

Table I Hemodynamic effects of nitroprusside hydralazine and hydralazine-nitrate combination in heart failure

Patient no	Heart rate (beats/min)					Mean systemic arterial pressure (mm Hg)					Mean pulmonary artery pressure (mm Hg)				
	C	NP	RC	H	H+N	C	NP	RC	H	H+N	C	NP	RC	H	H+
1	84	81	84	93	93	83	67	83	72	68	37	28	37	36	31
2	84	75	78	81	81	72	65	68	68	63	34	16	34	34	14
3	6J	67	69	72	75	77	58	74	77	65	37	32	3,	40	33
4	98	90	87	99	105	80	64	68	60	55	30	22	38	24	19
5	93	93	90	101	102	79	74	80	64	60	37	18	33	30	1
6	85	81	83	89	90	80	72	78	78	73	24	15	23	23	15
7	81	77	77	90	101	88	70	86	85	82	[illegible]0	39	52	57	51
8	84	72	72	84	81	87	65	75	82	68	51	35	40	4,	36
9	111	102	108	111	108	110	74	105	87	78	40	27	36	33	35
10	86	81	90	96	90	83	75	95	89	81	28	21	37	36	26
mean	88 0	81 9	83 8	91 6	92 6	83 9	68 4	81 2	76 2	69 3	36 8	25 3	36 7	36 0	35 3
SEM	3 7	3 3	3 5	3 5	3 6	3 3	1 8	3 7	3 2	2 9	2 8	2 6	2 3	3 9	3 3
p		< 001		< 001	< 01		< 001		NS	< 001		< 001		NS	< 0

C = control NP = nitroprusside RC = recontrol H = hydralazine H+N = hydralazine plus nitrate
= NP compared to C H compared to RC and H+N compared to RC

Table II Effects of nitroprusside hydralazine and hydralazine-nitrate combination on blood gases in heart failure

Patient no	Arterial PO (mm Hg)					Arterial PCO (mm Hg)					Venous PO (mm Hg)				
	C	NP	RC	H	H+N	C	NP	RC	H	H+N	C	NP	RC	H	H+N
1	77	80	77	80	80	22	23	22	17	17	27	30	27	30	31
2	3	6	65	82	58	35	34	37	28	38	31	35	31	34	31
3	9	71	84	73	71	40	36	35	40	39	28	29	28	28	[illegible]
4	73	6	8	72	64	28	33	33	29	28	26	28	27	33	30
5	87	6	84	86	82	31	35	34	31	29	36	42	38	45	39
6	85	60	80	91	75	32	31	33	33	32	35	31	35	38	34
7	71	68	80	73	62	3,	35	32	25	27	25	30	23	26	26
8	80	66	86	76	84	30	32	30	31	28	26	33	26	30	29
9	52	43	47	43	51	45	47	48	47	42	29	27	26	2,	31
10	76	63	70	75	70	37	38	41	37	36	28	32	23	30	31
mean	75 3	64 9	75 1	74 9	69 8	33 6	34 4	34 5	31 7	31 6	28 9	31 6	28 4	32 5	31 6
SEM	3 1	3 3	3 7	4 1	3 5	2.0	1 9	2 2	2 6	2 3	1 2	1 3	1 6	1 6	1
p		< 01		NS	NS		NS		05	NS		< 05		< 01	< 0

C = control NP = nitroprusside RC = recontrol H = hydralazine H+N = hydralazine-nitrate combination
= NP compared to C H compared to RC and H+N compared to RC

the interventions in each Per cent oxygen saturation was calculated from the PO and pH using an Instrumentation Laboratories pH blood gas calculator Alveolar-arterial oxygen difference (A-a gradient) in mm Hg was calculated according to the formula

$$A-a = P_AO_2 - P_aO_2$$

where P_aO_2 = arterial PO and P_AO_2 (PO of alveolar air) is calculated from the alveolar gas equation

$$P_AO_2 = P_IO - \frac{P_ACO_2}{R} + \left[\frac{P_ACO_2}{R} F_IO\ (1-R)\right]$$

with P_IO = inspired oxygen tension P_ACO = alveolar PCO (assumed equal to arterial PCO) F_IO = fraction of O in inspired air = 0 209 R = respiratory quotient (assumed = 0 8) Venous admixture (Q /Q) was calculated as

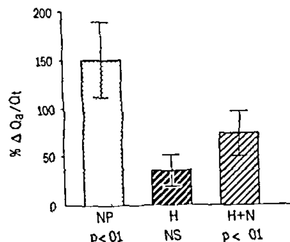


Fig 3 Per cent change in venous admixture *(Q /Q)* produced by nitroprusside *(NP)* hydralazine *(H)* and hydralazine nitrate combination *(H + N)* P values are given for comparing NP to control H to recontrol and H+N to recontrol *Horizontal bars* indicate mean ± SEM

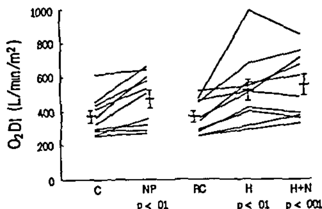


Fig 4 Changes in oxygen delivery index *(O DI)* produced by nitroprusside *(NP)* hydralazine *(H)* and hydralazine–nitrate combination *(H + N)* P values are given for comparing NP to control H to recontrol and H+N to recontrol *Horizontal bars* indicate mean ± SEM

P O with isosorbide dinitrate did not quite reach the $p < 0 5$ criteria for statistical significance ($t = 2\ 1954$ $p < 06$) Since the P O decreased with nitroprusside so did the calculated arterial oxygen saturation However due to the non linear relationship between P O and oxygen saturation the changes in oxygen content were of a much lower magnitude The values of arterial oxygen content measured directly paralleled the changes in O saturation but unfortunately these values were not available for every patient

The A a gradient (Fig 2) increased significantly with nitroprusside but not with hydralazine alone When isosorbide dinitrate was added the increase in A a gradient again became significant The changes in Q /Q paralleled those of the A a gradient and Fig 3 shows the per cent change in Q /Q which occurred with each regimen All of the patients had an increase in Q /Q with nitroprusside and Q /Q increased in nine of the ten patients with hydralazine plus isosorbide dinitrate but no significant changes occurred with hydralazine alone

The PO of mixed venous blood increased with all the drug regimens reflecting the increase in cardiac output There was a slight decrease in arterial PCO (P CO) with a concomitant increase in arterial pH after hydralazine and hydralazine–isosorbide dinitrate combination Although this decrease in P CO was small and only became statistically significant on the hydralazine–isosorbide dinitrate combination most of the decrease from recontrol levels had already occurred on the hydralazine alone This effect was not seen during nitroprusside infusion

Since the O DI (Fig 4) increased with all of the regimens it is evident that the rise in cardiac output compensated for the fall in P O such that oxygen delivery was not compromised This was true even in the patient with the most severe hypoxemia This patient had a control P O of 52 mm Hg that fell to 43 mm Hg on nitroprusside Despite this low level of P O his O DI went from 440 to 577 c c /min /M

Pulmonary function tests As seen in Table III no significant changes from control values were found in any of the pulmonary function tests (VC V V, V_m FEV_1 and SBN III) with any of the drugs In addition the V_D/V_T did not change with any of the drugs in those eight patients for whom it could be calculated

From the above data it appears that the major effects on arterial oxygenation occur with the drugs that have the most prominent pulmonary vascular effects (i e with nitroprusside and when isosorbide dinitrate is added to hydralazine but not with hydralazine alone) Fig 5 shows the correlation between change in A a gradient and change in PAR The correlation coefficient of this comparison is −0 57 which is significant at the 1 per cent level

Discussion

This study confirms the findings of Mookherjee and associates that a decrease in arterial PO occurs when patients with congestive heart failure are treated with nitroprusside This fall in P O occurs concomitant with an increase in A a

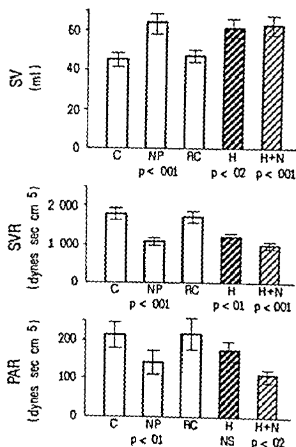


Fig 1 Changes in stroke volume *(SV)* systemic vascular resistance *(SVR)* and pulmonary arteriolar resistance *(PAR)* produced by nitroprusside *(NP)* hydralazine *(H)* and hydralazine nitrate combination *(H + N)* P values are given for comparing NP to control *(C)* H to recontrol *(RC)* and H+N to RC

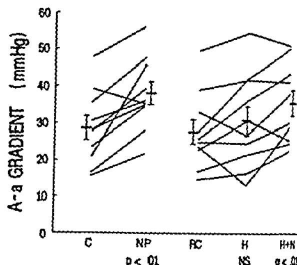


Fig 2 Changes in A a gradient produced by nitroprusside *(NP)* hydralazine *(H)* and hydralazine-nitrate combination *(H + N)* P values are given for comparing NP to control, H to recontrol, and H+N to recontrol *Horizontal bars* indicate mean ± SEM

dent s paired t test Data are presented as mean ± standard error of the mean Differences are considered statistically significant for p values less than 0 05

Results

Hemodynamics Hemodynamic responses to the different regimens are shown in Table I and Fig 1 presents the resultant effects on stroke volume (SV) SVR and PAR Nitroprusside increased CI and decreased $\overline{PA}$ and $\overline{PAW}$ pressure mean systemic blood pressure ($\overline{BP}$) and heart rate SV was increased while SVR and PAR decreased All hemodynamic parameters returned to the initial control levels after nitroprusside infusion was stopped except for a small but statistically significant decrease in heart rate

Hydralazine produced an increase in CI of 0 9 L/min/M and a fall in $\overline{BP}$ of 5 0 mm Hg without altering $\overline{PA}$ or $\overline{PAW}$ Heart rate increased modestly by 8 beats/minute As a result SV increased and SVR decreased but the small decrease in PAR was not significant

When isosorbide dinitrate was added to hydralazine the most significant changes were a decrease in $\overline{PA}$ and $\overline{PAW}$ resulting in a decrease in PAR of 61 dyn s cm from the level on hydralazine alone In addition there was a further 7 mm Hg decrease in $\overline{BP}$ and 180 dyn s cm decrease in SVR with essentially no additional increase in heart rate Except for a slight difference in heart rate there was no significant difference between the effects of hydralazine-isosorbide dinitrate combination and nitroprusside

Heart rate–systolic blood pressure product an index of myocardial oxygen consumption was not increased by any of the regimens From a control of 10 400 ± 952 (mean ± SEM) it decreased with nitroprusside to 8 440 ± 574 (p < 01) The values on hydralazine (9 570 ± 1212) and on hydralazine–nitrate combination (9 630 ± 671) were not significantly different from the post-nitroprusside recontrol value of 9 840 ± 862

Blood gases Table II summarizes the effects on blood gases of the different drugs and Figs 2 through 4 show the changes in A a gradient O /Q and O DI There are no significant differences in any of these variables between the initial control and the post nitroprusside recontrol values

P O fell significantly during nitroprusside infusion but not with hydralazine alone When isosorbide dinitrate was added to hydralazine the P O dropped by 5 1 mm Hg Compared to the post nitroprusside recontrol value this decrease in

combination despite the increase in A-a gradient.

Other vasodilators which affect pulmonary vasculature have also been shown to affect PO_2. Majid and colleagues used phentolamine to decrease the pulmonary arterial and pulmonary artery wedge pressures and increase the cardiac output in patients with severe heart failure. They observed a decrease in PO_2 from 72 ± 5 to 66 ± 5 mm Hg with the drug infusion at rest and from 73 ± 7 to 66 ± 7 mm Hg with the drug during exercise. In their patients unable to exercise, the PO_2 decreased from 64 to 60 mm Hg in the first five minutes of drug infusion. A similar effect was noted by Cournand and colleagues[1] using selective infusion of acetylcholine into one branch of the pulmonary artery as a vasodilator. Although Fritts and co-workers found no change in arterial oxygen saturation when infusing acetylcholine into the pulmonary artery of patients on 21 per cent oxygen, they did note a decrease when the patients were on 12 per cent oxygen.

The fall in PO_2 produced by nitroprusside has previously been attributed to an increase in venous admixture resulting from an altered ventilation/perfusion relationship in the lungs. Our observations support this, as the calculated venous admixture increased significantly with nitroprusside infusion and returned to control when it was stopped. No changes were found, however, in pulmonary mechanics. It is possible that other methods of determining pulmonary ventilation and perfusion abnormalities such as radioisotope or inert gas washout techniques would detect changes not apparent in our data. Nontheless our data do suggest that the major alterations in ventilation/perfusion occurred due to redistribution of flow rather than to changes in ventilation. The same mechanism is likely for the increase in A-a gradient produced by hydralazine plus isosorbide dinitrate.

Although time limitations precluded the testing of isosorbide dinitrate alone, it is known that isosorbide dinitrate does have a pulmonary vascular effect which hydralazine lacks. Thus an increase in A-a gradient and venous admixture might be expected to occur with isosorbide dinitrate alone in the absence of hydralazine effect. This hypothesis is supported by the finding that the closely related compound nitroglycerin has been shown to produce hypoxemia.

From the above considerations it is reasonable to postulate that vasodilators which affect the pulmonary vasculature act indiscriminately to dilate all pulmonary vessels including those perfusing poorly ventilated alveoli. This would alter the physiologic vasoconstrictor response which decreases blood flow to hypoventilated alveoli and thus upset the normal ventilation/perfusion balance. This becomes manifest by an increase in venous admixture and A-a gradient.

Other possible mechanisms for the decrease in PO_2 appear less likely. Hypoventilation is adequately ruled out by the lack of any increase in arterial PCO_2. Indeed, it is of interest that there was a small decrease in PCO_2 with a concomitant small increase in arterial pH when hydralazine was given that persisted when isosorbide dinitrate was added. This decrease in PCO_2 is unlikely a response to hypoxia, as little fall in PO_2 occurred with hydralazine and no similar decrease in PCO_2 occurred with nitroprusside despite the decrease in PO_2 produced by that drug.

Since an increase in cardiac output occurs with these vasodilators, it might be postulated that the transit time of blood in the lung is decreased such that it is not in contact with the alveolar gas exchange area long enough to become fully saturated. This would appear unlikely since full oxygen saturation is considered to occur in the early portion of the alveolar capillaries with adequate safety margin so that desaturation does not occur with the increase in cardiac output. In addition, hydralazine would be expected to increase A-a gradient similar to the other two drug regimens if this mechanism were operational, but A-a gradient did not change with hydralazine.

Another mechanism which could be considered is interference with biochemical reactions involving oxygen transport. However, it is unlikely that biochemical effects on hemoglobin function can account for the observed responses. Although the metabolites of nitroprusside (cyanide and thiocyanate) could be incriminated as possible effectors of hemoglobin function, similar compounds are not produced by the hydralazine plus isosorbide dinitrate combination which produced similar effects on A-a gradient and hemodynamics.

Although oxygen delivery was enhanced in all of our patients on vasodilators, we do not know the organ distribution of this increased flow. It is possible that some vascular beds may suffer from a lower oxygen content more than others due to redistribution of arterial blood. Since the

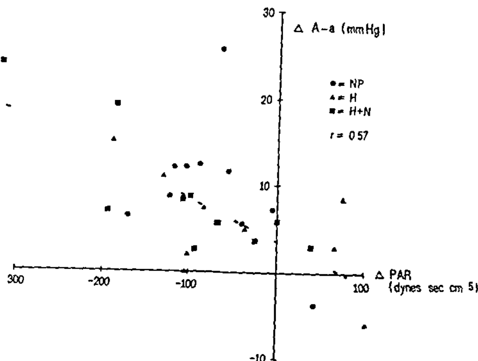


Fig 5 Correlation of change in alveolar-arteriolar oxygen gradient (Δ A-a) with change in pulmonary arteriolar resistance (Δ PAR) with nitroprusside (NP) hydralazine (H) and hydralazine plus isosorbide dinitrate (H+N) Correlation coefficient (r) = −0.57 which is significant at the 1 per cent level

Table III Effects of nitroprusside hydralazine and hydralazine-nitrate combination on pulmonary function tests in heart failure (mean ± SEM)

	Control	*Nitroprusside*	*Hydralazine*	*Hydralazine Nitrate*
FEV	19 ± 21	20 ± .20	19 ± .20	20 ± .0
III SBN	69 ± 261	69 ± 214	7.3 ± 260	82 ± 41
VC	31 ± 25	30 ± .30	29 ± 73	2.9 ± .84
V	40 ± 900	.34 ± 051	.50 ± 144	.58 ± 147
V	15 ± 36	1.3 ± .23	17 ± 40	17 ± 47
V	41 ± 61	39 ± .50	41 ± .57	42 ± 67
V /V	46 ± 041	45 ± .257	.39 ± 038	41 ± 023

FEV = forced expiratory volume at 1 sec in liters (10 patients) III SBN = slope of phase III of the single breath nitrogen test in % N /liter (8 patients) VC = vital capacity in liters (10 patients) V = flow at 25% of VC in liters/sec (10 patients) V = flow at 50% of VC in liters sec (10 patients) V = peak flow in liters/sec (10 patients) V /V = ratio of dead space to tidal volume (8 patients) None of the variables are significantly different from control with any of the drug regimens.

gradient Despite the decrease in P O and increase in A a gradient cardiac output improves such that calculated oxygen delivery is enhanced In addition this study demonstrates that although hydralazine produces an equivalent increase in cardiac output it has very little pulmonary vascular effects compared to nitroprusside Thus hydralazine has minimal effect on pulmonary artery pressure left ventricular filling pressure and PAR Also unlike nitroprusside hydralazine lacks any significant effect on P O or A a gradient

When isosorbide dinitrate is combined with hydralazine the venous and pulmonary vascular effects of the nitrate decrease pulmonary arterial pressure left ventricular filling pressure and PAR such that hemodynamic effects similar to nitroprusside are obtained Also similar to nitroprusside an increase in A a gradient is produced by the combination of hydralazine and isosorbide dinitrate Thus nitroprusside and the combination of hydralazine plus isosorbide dinitrate decrease PAR and increase A a gradient As with nitroprusside oxygen delivery is enhanced by the

The cyclic changes and structure of the base of the aortic valve

Mano Thubrikar Ph D
Stanton P Nolan M D
L Paul Bosher M D
J David Deck Ph D
Charlottesville Va

The base of the aortic valve is a circumferential region at the proximal attachment of the aortic leaflets It has been described as a fibrous annulus which suggests a ringlike nonexpansible structure The base has been reported to undergo little or no dimensional change during the cardiac cycle[1] Some investigators have stated that the annulus is not a continuous fibrous ring[5] [6] Others have speculated that the annulus does change dimensions and that it participates in aortic valve function[6] Furthermore the base of the aortic valve is continuous with the left ventricular outflow tract which changes in diameter during the cardiac cycle in humans[9] and in dogs

The previous reports indicate a disagreement on the behavior of the base of the natural aortic valve An accurate understanding of the behavior of the base is important If it is a dynamic structure its behavior will affect normal valvular function Current prosthetic valves are fabricated with a nonexpansile sewing ring which is attached to the base of the aortic valve If the base is a dynamic structure the mismatch with the nonexpansile ring could cause occasional periprosthetic leaks or could interfere with function of the base

The present study investigated the structure and behavior of the base of the aortic valve in dogs in vivo under physiologic conditions

Materials and methods

Four dogs (20 to 30 kg) were anesthesized with intravenous pentobarbitol (25 mg /kg) and placed on total cardiopulmonary bypass Through an aortotomy small platinum markers (1 mm × 1 mm and 10 mg weight) were attached to the annulus at the base of each aortic leaflet Small tantalum clips were also placed at the center of the free edge of two leaflets The position of the markers is shown in Fig 1 The dogs were allowed to recover and were studied repeatedly over several weeks

During each study the dogs were lightly anesthetized and were positioned under an x ray tube with an image intensifier During fluoroscopy the movements of the markers in the beating heart were recorded on videotape at a rate of 60 fields/second The marker movement was recorded first with the x ray beam parallel to the axis of the aorta (with the base markers projected in a triangle) and then with the x ray beam perpendicular to the axis of the aorta—(with the base markers projected in a straight line) Using these two projections it was possible to eliminate any error due to rotation or yaw of the aortic root The dog was then rotated 180 degrees on its spinal axis and the two new projections were recorded This enabled elimination of error due to movement of the aortic root toward or away from the image intensifier during the cardiac cycle The pressures in the ascending aorta and in the left ventricle were recorded using 7F pigtail catheters The EKG (Lead II) was also recorded simulta

From the Departments of Surgery and Anatomy University of Virginia Medical Center Charlottesville Va.

This work was supported by NIH Grants HL-17969 (Surgery) and HL-16935 (Anatomy)

Received for publication Dec 28 19 8.

Accepted for publication Feb 14 19"9

Reprint requests Mano Thubrikar Ph.D Box 181 Department of Surgery University of Virginia Medical Center Charlottesville Va. 22908.

0002 8703/80/0?0217 + 08$00.80/0 © 1980 The C V Mosby Co

decreases in oxygen content we observed are small this is unlikely to become clinically important except perhaps in patients with a very low initial P O Our patients had an increase in cardiac output with vasodilators but this might not occur in patients with initially normal cardiac outputs The possibility of significant global or regional hypoxia should thus be considered and blood gases should be monitored when vasodilators with prominent pulmonary vascular effects are used in patients who have a very low arterial PO and/or in whom no increase in cardiac output is expected

Summary

Nitroprusside (NP) has been shown to improve left ventricular function in patients with congestive heart failure but despite an increased cardiac output and decreased pulmonary capillary pressure, arterial oxygen tension (P O) may fall In order to determine the mechanism of this hypoxemia and to determine if similar effects occur with non parenteral vasodilators hemodynamic respiratory and blood gas responses to NP hydralazine (H) and hydralazine combined with isosorbide dinitrate (H+N) were studied in 10 patients with left ventricular failure At the dosages used all three drug regimens increased cardiac output equivalently but pulmonary vascular responses differed NP and H+N decreased mean pulmonary artery pressure pulmonary wedge pressure and pulmonary arteriolar resistance while H did not NP decreased P O by 10 4 mm Hg ($p < 01$) and H+N decreased it by 5 3 mm Hg ($p < 06$) while H did not alter P O Arteriolar-alveolar oxygen gradient increased with NP (150 ± 39 per cent $p < 01$) and with H+N (73 ± 23 per cent $p < 01$) but not H alone (51 ± 16 per cent) Similarly per cent change in venous admixture increased on NP (28 7 ± 3 3 to 38 5 ± 3 1 per cent $p < 01$) and H+N (28 1 ± 3 3 to 36 8 ± 3 5 per cent $p < 01$) but not H alone (28 1 ± 3 3 to 31 5 ± 4 1 per cent) There was no increase in arterial carbon dioxide tension or change in pulmonary function studies with any of the drugs Due to the increase in cardiac output oxygen delivery index (cardiac output times arterial oxygen content) increased with each regimen despite the changes in P O Changes in arteriolar-alveolar oxygen gradient correlate with the changes in pulmonary arteriolar resistance Thus vasodilators which have prominent pulmonary vascular effects can de[crease] P O in patients with congestive heart failur[e] this effect is most likely due to increasing ve[ntila]tion-perfusion inequities

We wish to acknowledge the technical assistance of P[...] Heckel and the secretarial help of Margaret Chelmo[...] preparation of this manuscript

REFERENCES

1 Griffiths D P G Cummings B H Greenbau[m] Griffith H B Staddon G E Wilkins D G and J S M Cerebral blood flow and metabolism [...] hypotension induced with sodium nitroprusside [...] Anaesth 46 671 1974
2 Wildsmith J A W, Drummond G B and Macr[ae] R Blood gas changes during induced hypotension [...] sodium nitroprusside Br J Anaesth 47 1205 19[...]
3 Brodie T S Gray R Swan H J C and Matloff [...] Effects of nitroprusside on oxygenation intrapul[monary] shunts and oxygen delivery (Abstract) Am J Ca[rdiol] 37 123 1976
4 Mookherjee S Keighley J Warner R A Bras[...] A and Obeid A I Hemodynamic ventilatory [and] blood gas changes during infusion of sodium nitro[ferri]cyanide (nitroprusside) studies in patients with co[nges]tive heart failure Chest 72 273 1977
5 Chatterjee K Parmely W W Massie B Green[berg] B Werner J Klausner S and Norman A [...] hydralazine therapy for chronic refractory heart fa[ilure] Circulation 54 879 1976
6 Franciosa J A Pierpont G and Cohn J N Hem[ody]namic improvement after oral hydralazine in left ven[tric]ular failure A comparison with nitroprusside infusio[n in] 16 patients Ann Intern Med 86 388 1977
7 Mikulic E Franciosa J A and Cohn J N Comp[ara]tive hemodynamic effects of chewable isosorbide d[ini]trate and nitroglycerin in patients with congestive h[eart] failure Circulation 52 477 1975
8 Pierpont G Cohn J N and Franciosa J A Hem[ody]namic equivalency of oral hydralazine-isosorbide d[ini]trate combination and intravenous nitroprusside in [left] ventricular failure Chest 73 8 1978
9 Majid P A Sharma B and Taylor S H Phen[tol]amine for vasodilator treatment of severe heart failu[re] Lancet 2 719 1971
10 Cournand A Fritts H W Jr Harris P and Him[mel]stein A Preliminary observations on the effects in m[an] of continuous perfusion with Acetylcholine of one bran[ch] of the pulmonary artery upon the homolateral pul[mo]nary blood flow Trans Assoc Am Physicians 69 [...] 1956
11 Fritts H W Harris P Clauss R H Odell J E a[nd] Cournand, A The effect of Acetylcholine on the hum[an] circulation under normal and hypoxic conditions, J C[lin] Invest 37 99 1958
12 Mookherjee S Fulhelhan D Warner R A Vardan [...] and Obeid A I Effects of sublingual nitroglycerin o[n] resting pulmonary gas exchange and hemodynamics [in] man Circulation 57 106 1978
13 Staub N C Alveolar-arterial oxygen tension gradie[nt] due to diffusion J Appl Physiol 18 673 1963

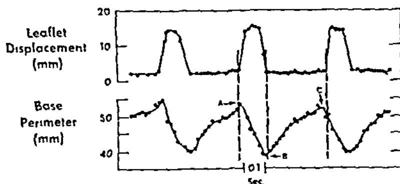


Fig 2 Phasic plot of leaflet displacement (the distance between the two leaflet markers) and base perimeter (perimeter of a triangle formed by the base markers) versus time The base perimeter is maximum (point A) in early systole The perimeter decreases (A to B) in systole and increases (B to C) in diastole

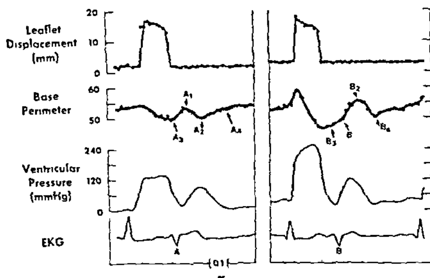


Fig 3 Phasic plot of leaflet displacement base perimeter corresponding ventricular pressure and EKG versus time for two separate recordings Two normal heartbeats and two ectopic beats (A and B) are shown For the normal beats the base perimeter decreases during systole For ectopic beat A the perimeter decreases (A to A) but for ectopic beat B the perimeter increases (B to B) during systole. Base perimeters were greater after the ectopic beats (A and B) than before the beats (A and B)

pressure was varied over a wide range the change in the perimeter also varied In four dogs when the pressure was varied from 70/50 to 280/216 mm Hg the change in the perimeter ranged from 5% to 28% (Table I)

With premature ventricular contractions the behavior of the base could vary from that observed in normal cardiac cycles (Fig 3) During ectopic beat A the base perimeter decreased from A to A (during systole) During B the perimeter increased from B to B (during systole) The ventricular pressure increased in both instances During both ectopic beats no blood was ejected (the leaflets did not open) and the base perimeter was greater after these ectopic beats (A, and B) than before (A_3 and B) The base perimeter increased in every dog as the ventricular diastolic pressure increased (Fig 4)

Histologic examination of the aortic root indicated that the structure would permit the dimensions of the base to change during the cardiac cycle Transverse sections of the root showed that contractile tissue either musculoelastic tissue or myocardium comprises portions of the root at the base For example a section through the middle of the root which illustrated all parts of

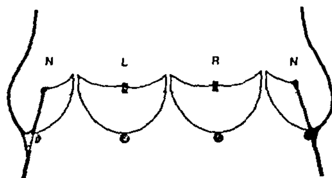


Fig 1 Aortic valve exposed by a vertical incision through the noncoronary sinus *L R* and *N* are the leaflets corresponding to the left right and noncoronary sinuses respectively *Dotted line* shows the level of leaflet coaptation Three radiopaque markers at the base of the leaflets are represented by *closed circles* Two radiopaque markers at the center of the free edge of the left and right coronary sinus leaflets are represented by *vertical bars*

Table I Blood pressure vs base perimeter

Dog No	*Blood pressure (mm Hg)*	*Base perimeter change*
1	Aortic 120/60	2? ± ?
2	Aortic 1??/90	16 ± 1.5
3	Aortic 113/78	8.8 ± 1.8
4	Femoral 108/8?	9.6 ± 2
	Mean 115/78	Range 9 to 22
Aortic blood pressure		
1	70/50 260/160	5 10
2	94/48 255/150	10 16
	90/35 270/187	6.5 1?
3	88/50 25?/216	10-18
	120/60 240/210	?0 ?8
4	?0/4? ?80/156	1 28
	Range 70/50 280/216	Range 5 to ?8

Base perimeter % change $= \frac{P\ max - P\ min}{P\ min} \times 100\%$
(where P = perimeter)

neously with the videotape recording The systemic pressure was raised by infusing angiotensin or lowered by infusing nitroprusside and the studies were repeated

The movement of the leaflets and dimensional changes of the base were obtained by analysis of the movement of the markers The videotapes were analyzed field by field in a stop motion display mode on a television screen In the first projection recorded with the x ray beam parallel to the axis of the aorta the distance between the two leaflet markers was measured in each frame for three consecutive cardiac cycles This distance was used as an indicator of a closed or opened valve The perimeter of the triangle formed by the base markers was also measured and was used as an indicator of the dimensions of the base

A typical graphic representation of the leaflet displacement plotted as the distance between two leaflet markers and the base perimeter versus time is shown in Fig 2 Each data point on these curves was obtained from a single videofield

In the second projection recorded with the x ray beam perpendicular to the axis of the aorta the analysis of the movement of the markers was performed in a manner similar to that used for the first projection Details of the analysis are given elsewhere The movement of the leaflets and the dimensional changes in the base obtained from this projection were similar to those obtained from the first projection

The structure of the base was studied histologically in canine aortic roots which were subserially sectioned and fixed in the closed position with glutaraldehyde at 100 mm Hg pressure The sections were stained to show the distribution of collagenous elastic and muscular elements of the valve

Results

Dimensional changes of the base The base of the aortic valve changed dimensions during each normal cardiac cycle (Fig 2) The base perimeter was maximal (point *A*) in early systole just prior to separation of the leaflets The perimeter decreased (interval *AB*) during systole and was minimal (point *B*) at the end of systole just prior to approximation of the leaflets The perimeter increased (interval *BC*) during diastole This qualitative behavior of the base was observed consistently in all dogs and in all normal cardiac cycles

The amount of the cyclic change in the base perimeter was calculated by measurement of the peak to peak values (*A* to *B*) The amount of cyclic change at normal systemic pressure was determined for each dog by taking an average of 24 to 36 cardiac cycles obtained from two to three separate studies The amount of cyclic change at other systemic pressures was determined by taking an average of six to nine cardiac cycles obtained from two to three separate studies The amount of change was different for different dogs at normal systemic pressure In four dogs the change in the perimeter ranged from 9% to 22% (Table I) In any one animal when the systemic

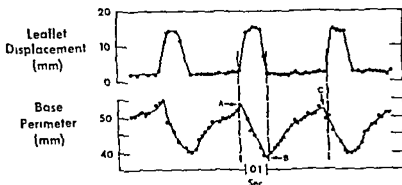


Fig 2 Phasic plot of leaflet displacement (the distance between the two leaflet markers) and base perimeter (perimeter of a triangle formed by the base markers) versus time The base perimeter is maximum (point *A*) in early systole The perimeter decreases (*A* to *B*) in systole and increases (*B* to *C*) in diastole

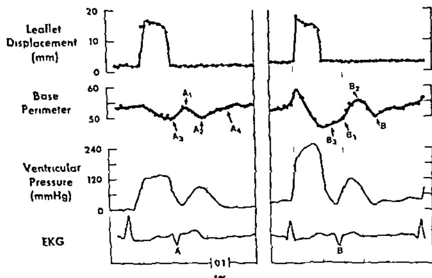


Fig 3 Phasic plot of leaflet displacement base perimeter corresponding ventricular pressure and EKG versus time for two separate recordings Two normal heartbeats and two ectopic beats (*A* and *B*) are shown For the normal beats the base perimeter decreases during systole For ectopic beat *A* the perimeter decreases (*A* to *A*) but for ectopic beat *B* the perimeter increases (*B* to *B*) during systole Base perimeters were greater after the ectopic beats (*A* and *B*) than before the beats (*A* and *B*)

pressure was varied over a wide range the change in the perimeter also varied In four dogs when the pressure was varied from 70/50 to 280/216 mm Hg the change in the perimeter ranged from 5% to 28% (Table I)

With premature ventricular contractions the behavior of the base could vary from that observed in normal cardiac cycles (Fig 3) During ectopic beat *A* the base perimeter decreased from *A* to *A* (during systole) During *B* the perimeter increased from *B* to *B* (during systole) The ventricular pressure increased in both instances During both ectopic beats no blood was ejected (the leaflets did not open) and the base perimeter was greater after these ectopic beats (*A* and *B*) than before (*A* and *B*) The base perimeter increased in every dog as the ventricular diastolic pressure increased (Fig 4)

Histologic examination of the aortic root indicated that the structure would permit the dimensions of the base to change during the cardiac cycle Transverse sections of the root showed that contractile tissue either musculoelastic tissue or myocardium comprises portions of the root at the base For example a section through the middle of the root which illustrated all parts of

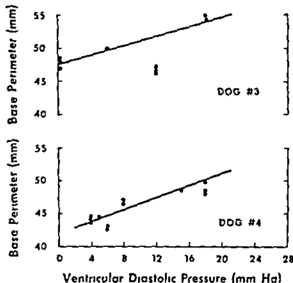


Fig 4 Base perimeter in diastole versus ventricular diastolic pressure for two dogs The base perimeter increases as the ventricular diastolic pressure increases

the valve (Fig 5 *a*) showed sinus walls composed principally of smooth muscle interwoven with elastic connective tissue fibers like the more distal wall of the aorta itself Segments of wall between the sinuses (called intervalvular trigones by McAlpine[11]) are composed of dense collagenous tissue (*d* in Fig 5 *a*) or myocardium (Fig 5 *a* and *c* in Fig 5 *b*) plus a more internal cushion of very loose watery connective tissue (Fig 5, *a* and *u* in Fig 5 *b*) Much of this myocardial mass consists of circularly oriented fibers (*c* in Fig 5 *b*) some of which appear to be inserted into the sinus wall (Fig 5 *b arrow*) Contraction of this muscle tends to decrease the circumference of the root More proximally toward the base of the valve two of the three trigonal regions consist almost entirely of obliquely or circularly oriented myocardium (*c* in Fig 6 *a*) Dense collagenous tissue present in these zones is limited to a thin intimal layer of tissue (*i* in Fig 6 *b*) internal to the loose connective tissue cushion (*w* in Fig 6 *b*) and continuous with the ventricular face of the valve leaflets This tissue is neither as dense nor as thick as the major substances of the leaflets themselves Only the trigonal region between the left coronary and the noncoronary sinuses which serves as the origin of a mitral valve leaflet is composed of dense collagenous tissue throughout the aortic root (Figs 5 *a* 6 *a* 7 *a* and *d* in Fig 7 *b*) At their bases where the markers were placed (Fig 7 *a* and *l* in Fig 7 *b*) the right and left coronary leaflets appear to be embedded in ventricular muscle (*c* in Fig 7, *a*) Frequently the noncoronary leaflet is the shallowest of the three and its base appears higher in the root (Fig 6, *a*) than the base of the other two leaflets (*l* in Fig 7 *a*) Dense fibrous tissue does not form a circular investment of the entire aortic root at any of the levels described This is especially true at the level of the leaflet bases

Discussion

The cyclic changes in the dimensions of the base of the aortic valve are similar to the changes in left ventricular geometry and volume in a normal cardiac cycle (Fig 2) The base perimeter is maximal in early systole This coincides with rounding of the ventricular cavity known to occur during isovolumetric contraction[17] The base perimeter decreases during systole This coincides with the decrease in ventricular volume during systolic ejection The perimeter is minimal at the end of systole The perimeter increases during diastole This coincides with the increase in the ventricular volume due to diastolic filling

Although the changes of the base perimeter are similar to the known changes of left ventricular geometry and volume qualitatively throughout the normal cardiac cycle a quantitative correlation between the base perimeter and the ventricular pressure in systole was not observed This lack of quantitative correlation may be explained as follows In systole, the behavior of the base is a combination of two factors passive expansion (due to increased ventricular pressure) and active contraction (due to active tension in the base). Since these factors change in magnitude and relative proportion throughout systole their effect on base behavior is constantly variable For example in Fig 3 one may see that in ectopic beat *A* the base contracts, whereas in ectopic beat *B* the base expands although ventricular pressure is increasing in both instances

There is a quantitative correlation between the base perimeter and the ventricular pressure in diastole (Fig 4) The base of the aortic valve is relaxed and therefore expands passively in response to increasing ventricular diastolic pressure This correlation is also indicated by the following observations During both ectopic beats *A* and *B* (Fig 3) in which no blood was ejected (the leaflets did not open) the base perimeter was greater after the beats than before The diastolic

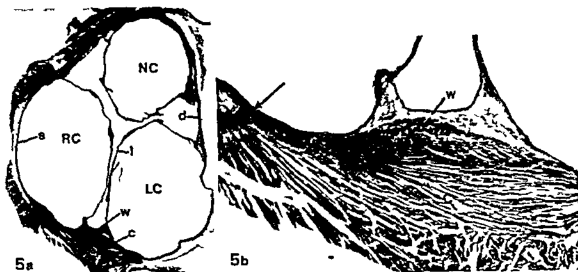


Fig 5 *a* Transverse section of aortic root approximately halfway between base at ventricle and sinus rims. Section shows three leaflets enclosing corresponding aortic sinuses and leaflet attachments to the wall The root wall at this level consists of smooth muscle-elastic tissue *(s)* myocardium *(c)* or dense collagenous tissue *(d)* (Original magnification ×2.5) *b* Enlargement from 5 *a* of intervalvular trigonal region between right and left coronary leaflets The root wall consists predominantly of circularly oriented myocardium some fibers of which insert into the sinus wall (Original magnification ×12.)

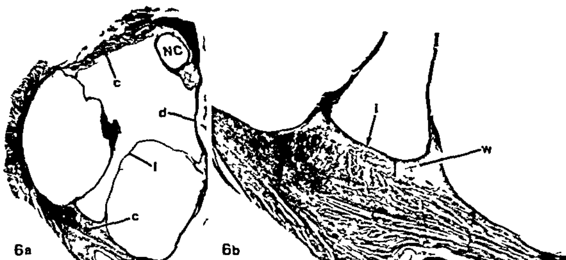


Fig 6 *a* Transverse section of aortic root near base of noncoronary leaflet At this level myocardium *(c)* makes up most of the wall tissue of two of the three trigonal regions and invests the wall of the right coronary sinus as well (Original magnification ×3) *b* Enlargement from 6, *a* of trigonal region between right and left leaflets. *Masses of myocardium fill the space between walls of the two sinuses bounded internally by a very loose watery* connective tissue *(u)* and an extremely thin intimal layer of denser tissue *(i)* curved onto the ventricular face of each leaflet. (Original magnification ×10)

ventricular pressure and volume would also be expected to be greater after these abnormal beats than before

Since the base of the aortic valve undergoes a consistent dimensional change during each normal cardiac cycle it must participate in normal aortic valve function During opening of the aortic valve expansion of the base to its maximum perimeter displaces the leaflet attachments outward This change and the expansion of commissures observed in previous studies[13] would *eliminate the zone of* leaflet redundancy (Fig 8 *A*)



Fig 7 *a* Transverse section of aortic root at level of junction between ventricle and the two coronary leaflets of valve Markers were placed at leaflet bases approximately at this level of the root (and somewhat more distally beneath the noncoronary leaflet which is more shallow and therefore was not cut by this section) Basal tissue of leaflets *(l)* consists of the same very loose watery connective tissue noted in previous figures The myocardium which comprises the wall between the leaflet bases represents a distal extension of the interventricular septum (Original magnification ×3) *b* Enlargement from 7 *a* of the region between bases of the two coronary leaflets Sectioning artifacts partially obscure the direction of constituent fibers but the dominant tissue is myocardium Dense fibrous tissue *(d)* to the side of the left leaflet base *(l)* serves as the origin of one of the mitral valve leaflets (Original magnification ×8 5)

The entire leaflet can then move to the open position without bending in the radial direction In the absence of expansion of the base as may occur with bioprostheses with nonexpansile sewing rings the load bearing portion of the leaflet would be displaced initially by the ventricular pressure creating increased bending at the line of coaptation (Fig 8 *B*) During closure of the normal aortic valve the contraction of the base to its minimum perimeter displaces the leaflets inward This reduces the distance the leaflets must travel to close the valve (Fig 8 *C*) and also assures complete closure of the orifice In the absence of contraction of the base (i e bioprostheses with a nonexpansile base) the valve closure may be delayed (Fig 8 *D*) In fact the closure may not occur until reversed flow is established The leaflets would then have to arrest the momentum of the blood and this would produce additional stresses in the leaflets [1]

These results agree with those suggested by some investigators but differ from those observed by others Swanson and Clark using Silastic root casts of the aortic valve observed a 10% change in the base diameter over a pressure range of 20 to 120 mm Hg Mercer[4] studied aortograms performed on humans and observed no change in the aortic valve annulus diameter Zimmerman[1] and Reid on observation of structure speculated that the annulus does not change diameter In contrast we have demonstrated that the base changes dimensions throughout the cardiac cycle in a manner similar to the changes in ventricular volume and the magnitude of change ranges from 5% to 28% over a wide range of systemic pressures (Table I)

The base of the aortic valve is capable of cyclic dimensional changes because it is partly composed of ventricular myocardium (Fig 7 *a*) At the base two of the three trigonal regions consist of myocardium and the right and left coronary leaflets and sinuses are encompassed by myocardium (Fig 6 *a*) Ventricular myocardium also forms part of the mitral valve annulus Hinds and associates observed that the mitral valve annulus changed dimensions throughout the cardiac cycle The dimensional changes of the mitral valve annulus reported by them are similar to those of the base of the aortic valve suggesting that similar forces are responsible for these changes Since both the mitral valve and the

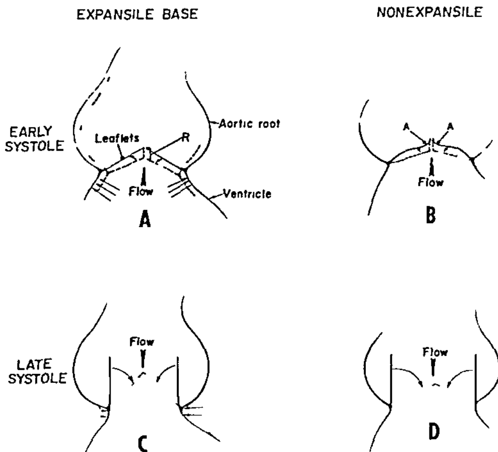


Fig 8 A schematic presentation of the side view of the aortic valve *A* Solid lines indicate expansile base and dotted lines indicate nonexpansile base Expansion of the base (indicated by arrows in the ventricle) prior to the opening of the valve causes the leaflets to move from their old position *(dotted lines)* to their new position *(solid lines)* This eliminates the zone of leaflet redundancy *(R)* *B* In case of a nonexpansile base the increase in the ventricular pressure prior to the opening of the valve causes the leaflets to move from their old position *(dotted lines)* to their new position *(solid lines)* by a process of bending This creates greater bending at the line of coaptation (indicated by *A*) *C* Contraction of the base (indicated by *arrows* in the ventricle) prior to the valve closure displaces the leaflets inward This reduces the distance the leaflets have to travel to close (from *solid lines* to *dotted lines*) *D* In case of a noncontractile base the leaflets have to travel a larger distance This may delay the valve closure

aortic valve are attached to the ostium of the left ventricle [6] changes in the dimensions of the ostium would produce similar changes in the aortic valve base and the mitral valve annulus

These changes may be important in the design of valvular bioprostheses If a bioprosthesis with a nonexpansile sewing ring is attached to the base of the aortic valve cardiac contraction would produce shearing strain on the sutures and could cause suture breakdown or dehiscence producing a periprosthetic leak

Summary

The structure and behavior of the base of the aortic valve in the dogs were investigated The structure was studied under light microscopy to determine the distribution of collagenous elastic and myocardial elements The dimensional changes were studied in vivo by attaching radio paque markers to the base and observing their movement by x ray studies The base is partly composed of ventricular myocardium Two of the three trigonal regions consist of myocardium and the right and left coronary leaflets and sinuses are encompassed by ventricular myocardium The collagenous tissue that lies internal to the myocardium is neither dense nor thick and does not form a complete ring The cyclic dimensional changes in the base are similar to the cyclic changes in left ventricular geometry and volume

The base perimeter is maximal in early systole coincident with the rounding of the ventricular cavity during isovolumetric contraction The base perimeter decreases during systole when the ventricular volume decreases during systolic ejection The base perimeter increases during diastole as the ventricular volume increases due to diastolic filling The amount of cyclic change in the base perimeter at normal systemic pressure was different for different dogs In four dogs the amount of change varied from 5% to 28% over a wide range of systemic pressures The importance of the behavior of the base in normal valvular function is discussed It is speculated that the mismatch between the nonexpansile sewing ring of an aortic bioprosthesis and the normally expansile base of the valve could cause occasional periprosthetic leaks

REFERENCES

1 Zimmerman J The functional and surgical anatomy of the aortic valve Cardiac Surg 5 862 1969
2 Reid K The anatomy of the sinus of valsalva Thorax 25 79 1970
3 Swanson W M and Clark R E Dimensions and geometric relationships of the human aortic valve as a function of pressure Circ Res 35 871 1974
4 Mercer J L Movement of the aortic annulus Br J Radiol 42 623 1969
5 McAlpine W A Heart and Coronary Arteries New York, 1975 Springer Verlag p 9
6 Davila J C The mechanics of the cardiac valves, in Merendino K A editor) Prosthetic Valves for Cardiac Surgery Springfield Ill 1961 Charles C Thomas, Publishers p 3
7 Padula R T Cowan G S M and Camishion, R C Photographic analysis of the active and passive components of cardiac valvular action J Thorac Cardiovasc Surg 56 790 1968
8 Tsioubas T Calibre variations in the left ventricular outflow tract Acta Radiol [Diagn] (Stockh) 3 909 1965
9 Ross J Sonnenblick E H Covell J W Kaiser G A and Spiro D The architecture of the heart in systole and diastole Circ Res 21 409 1967
10 Thubrikar M Harry R R and Nolan S P Normal aortic valve function in dogs Am J Cardiol 40 563, 1977
11 McAlpine W A Heart and Coronary Arteries New York 1975 Springer Verlag p 19
12 Rushmer R F Cardiovascular Dynamics Philadelphia 1976 W B Saunders Co p 53
13 Thubrikar M Bosher L P Harry R R and Nolan S P The mechanism of opening of the natural aortic valve in relation to the design of trileaflet prostheses, Surg Forum 28 264 1977
14 Spaan J A E Steenhoven A A Schaar P J Dongen M E H Smulders P T and Leliveld W H Hydrodynamical factors causing large mechanical tension peaks in leaflets of artificial triple leaflet valves Trans Am Soc Artif Intern Organs 21 396 1975
15 Hinds J E Hawthorne E W Mullins C B and Mitchell J H Instantaneous changes in the left ventricular lengths occurring in dogs during the cardiac cycle Fed Proc Am Soc Exp Biol 25 1351 1969
16 McAlpine W A Heart and Coronary Arteries New York 1975 Springer Verlag p 18

Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978 Therefore all manuscripts must be accompanied by the following written statement signed by one author The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C V Mosby Company in the event the work is published The undersigned author warrants that the article is original is not under consideration by another journal and has not been previously published I sign for and accept responsibility for releasing this material on behalf of any and all co authors Authors will be consulted when possible regarding republication of their material

Case reports

Rupture of a papillary muscle of the tricuspid valve in primary pulmonary hypertension

K Kunhali M D D M (Card)
George Cherian M D D M (Card) F A C C F A M S
A Bakthaviziam M D (Path)
M Thomas Abraham M D
S Krishnaswami M D D M (Card) F A C C
Vellore India

Rupture of a papillary muscle of the tricuspid valve (RPM TV) is rare and generally less dramatic than mitral papillary muscle rupture[1] The usual causes of RPM TV are trauma infective endocarditis and myocardial infarction occasionally cardiopulmonary resuscitation may also result in this complication In all these circumstances there is direct damage to the papillary muscle and or chordae which predisposes to or precipitates a rupture To our knowledge spontaneous rupture of an otherwise normal papillary muscle of the tricuspid valve has not been reported in the English literature to date We have recently studied a case of primary pulmonary hypertension (PPH) with spontaneous rupture of a tricuspid papillary muscle

Case report

G P a 75 year old farmer entered the hospital on November 1 19 with a 3 year history of dyspnea on effort In March 19 while cycling he abruptly developed chest discomfort and breathlessness he noticed for the first time a humming noise in his chest This continued until the terminal event His effort tolerance decreased rapidly and he developed frequent episodes of paroxysmal nocturnal dyspnea (PND) orthopnea and swelling of the legs

During the preceding 3 years he had experienced two episodes of arthralgia involving the knee joints accompanied by fever but no other joint was involved There was no history of chest trauma pain suggestive of myocardial infarction hemoptysis venous thrombosis surgical procedures pulmonary embolism or Raynaud's phenomenon He had never stayed at high altitude or consumed weight reducing drugs or any indigenous medicines A family history of primary pulmonary hypertension was not obtained

Clinical examination revealed a mildly jaundiced poorly nourished man weighing 6 pounds He was orthopneic and his extremities were cold and cyanotic There was no evidence of thrombophlebitis varicose veins, or edema His pulse rate was 112/minute and regular with a low volume blood pressure 95/ 0 mm Hg respiratory rate 28 minute and oral temperature 37 C Jugular venous pressure at 90 degrees was elevated up to the angle of the mandible and showed large CV waves There was cardiomegaly with a hyperdynamic apical impulse in the fifth left intercostal space internal to the anterior axillary line There was a moderate left parasternal lift with a systolic thrill felt all over the precordium but best felt along the lower left sternal border (LLSB) The first heart sound was normal and the second sound was obscured by a loud holosystolic murmur A right ventricular gallop (S) was present A harsh 5 6 holosystolic murmur was audible all over the precordium with maximum intensity at the LLSB but well heard at the apex and left axilla There was no appreciable change in the intensity of the murmur with respiration or physical maneuvers The lungs showed bilateral rales and the liver was enlarged and tender

The total leukocyte count was 5 500 mm with a differential of 54% polymorphs 42% lymphocytes and 4% monocytes Erythrocyte sedimentation rate was 3 mm /hour and hemoglobin 17 5 gm./100 ml. with a hematocrit of 53% Antistreptolysin O titer was 340 units blood urea 24 mg /100 ml serum bilirubin 3 2 mg /100 ml (direct reacting being 1 8 mg 100 ml.) serum glutamic oxaloacetatic transaminase 11 units The scalar electrocardiogram (Fig 1) showed a sinus tachycardia with a heart rate of 115/minute right and left atrial enlargement right ventricular hypertrophy with repolarization changes in right chest leads and clockwise rotation The frontal plane QRS axis was +10 degrees

An x ray film of the chest (Fig 2) showed a cardiothoracic ratio of 0 74 an enlarged right atrium normal aortic shadow and markedly enlarged pulmonary arteries, the right descend

From the Departments of Cardiology and Pathology Christian Medical College and Hospital

Received for publication Sept 6 19 8
Accepted for publication Nov 8 19 8

Reprint requests George Cherian M D Head Cardiology Department Christian Medical College Hospital, Vellore 632 004 India

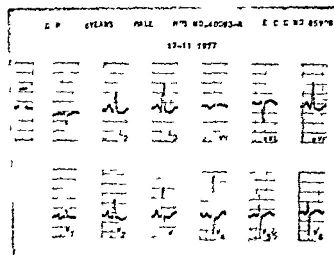


Fig 1 Electrocardiogram showing right and left atrial enlargement and right ventricular hypertrophy with clockwise rotation

Table 1 Hemodynamic data

Site	Pressure (mm Hg)	Oxygen saturation (%)
Superior vena cava	–	45 0
Right atrium	CV 26 y 11 m 18	44 5
Right ventricle	8[illegible]/0 16	44 5
Pulmonary artery	82/[illegible] m 64	4[illegible] 0
Left ventricle	101/0-6	
Aorta	101/70 m 81	8[illegible] 0 (98 0 on [illegible] administration for 10 min)
Cardiac index (L/min/m)		[illegible]
Pulmonary vascular resistance (dynes sec/cm)		29[illegible]
Sytemic vascular resistance (dynes sec/cm)		32[illegible]

Abbreviations cv and y denote respective points on the atrial pres[illegible] curves m = mean LV edp = Left ventricular end-diastolic pres[illegible]

ing branch measuring 22 mm in diameter There was peripheral pruning of the pulmonary arteries No left atrial enlargement could be made out by barium esophagram in the right anterior oblique (RAO) projection

He slowly improved with conventional treatment and cardiac catheterization and selective cineangiography were carried out on the twenty-seventh hospital day under premedication with promethazine (25 μg intramuscularly) and phenobarbital (50 μg intramuscularly) with a provisional diagnosis of acute mitral regurgitation Left ventriculography was done in the RAO projection followed by right ventricular and pulmonary arteriography The patient later developed persistent hypotension and expired 3 hours after cardiac catheterization A partial autopsy was obtained and heart lungs and viscera were examined

Hemodynamic data are detailed in Table I and Fig 3 and 4 There was ventricularization of the right atrial tracing with [illegible] CV waves Right ventricular end-diastolic pressure (RV edp) was markedly elevated and the pulmonary artery pressures were near systemic level The left ventricular end diastolic pressure was normal Cardiac index was low with systemic arterial desaturation

A left ventriculogram showed no mitral regurgitation A right ventricular angiogram showed marked enlargement of the right ventricle with severe tricuspid regurgitation and a large right atrium A pulmonary arteriogram showed marked dilatation of the main pulmonary artery and its major branches with peripheral pruning There was no [illegible] of the pulmonary arteries

At autopsy the heart weighed [illegible] The right atrium was markedly dilated and thin [illegible] The right ventricle showed marked hypertrophy [illegible] The right ventricular free wall [illegible] the septum 10 mm The [illegible] 14 cm The septal papillary [illegible] ruptured at the chordopapillary junction [illegible] muscles appeared normal on gross examination [illegible] cusps were smooth The right ventricular [illegible] dilated The pulmonary valve measured [illegible]

pulmonary artery and its major branches were dilated [illegible] showed artheromatous lesions There were no thrombi in [illegible] pulmonary arteries The left atrium was normal and [illegible] mitral valve measured 7 cm The left ventricular cavity [illegible] normal in size and the aortic valve measured 5 5 cm The ao[illegible] was normal Macroscopic examination of the liver and sp[illegible] showed evidence of marked chronic venous congestion

The sections from the right ventricle showed evidence [illegible] hypertrophy of muscle fibers with focal areas of intert[illegible] fibrosis The ruptured papillary muscle showed no ac[illegible] degenerative changes and appeared similar to other papi[illegible] muscles of the right ventricle showing patchy fibrosis T[illegible] lungs showed well marked evidence of pulmonary hypert[illegible] sion There was widespread medial hypertrophy and int[illegible] proliferation with many plexiform (Fig 6 A) and dilata[illegible] (Fig 6 B) lesions

Discussion

Rupture of a papillary muscle is a relativ[illegible] rare cardiac lesion In the vast majority of ca[illegible] it occurs on the left side as a complication [illegible] acute myocardial infarction Little is known [illegible] the real incidence etiology and natural histor[illegible] rupture of papillary muscle of the tricu[illegible] valve The condition was first clinically di[illegible] nosed by Parmley and associates in 1958 i[illegible] patient with nonpenetrating trauma to the che[illegible] In 1977 Gerry and colleagues could collect o[illegible] nine cases of RPM TV from the English lite[illegible] ture to which they added two of their own T[illegible] relative scarcity of reported cases of RPM TV [illegible] comparison to the left side may be at least in p[illegible] due to the less dramatic clinical presentation a[illegible] the difficulties in establishing a firm diagno[illegible] the former



Fig 2 *A* Posteroantenor chest radiograph. Note marked dilatation of the right atrium and the proximal pulmonary arteries *B* Esophagram in right anterior oblique projection showing no evidence of left atrial enlargement

In 7 out of the 11 reported cases RPM TV resulted from trauma to the chest it followed infective endocarditis in three cases and myocardial infarction in one This is in sharp contrast to left sided RPM which in the majority of patients results from acute myocardial infarction Although there are reports of acute tricuspid regurgitation following myocardial infarction RPM TV has been confirmed only in one case to date While spontaneous rupture of an otherwise normal papillary muscle is known to occur on the left side we are unaware of any reported instance of such an occurrence on the right side

In our patient who had PPH the RPM TV occurred spontaneously Gerry and associates point out that the increased wall tension in a dilated ventricle leads to increased tension in papillary muscles and chordae tendinae and thus predisposes to their rupture and in the present case RPM TV occurred during cycling Interestingly in this case the ruptured and unruptured papillary muscles on the right side showed no significant histologic differences and the rupture was at the chordopapillary junction unlike those associated with acute myocardial infarction or trauma

Primary pulmonary hypertension is not an uncommon clinical entity in India A report of 91 cases of pulmonary hypertension has been recently presented from this center and unexplained PND was present in 10% Although the pathogenesis is not clear PND has been reported in patients with isolated tricuspid insufficiency [6] As the pulmonary lymphatics empty into the systemic veins any sudden elevation of the central venous pressure could impede pulmonary lymphatic drainage resulting in pulmonary congestion [11] Uhley and associates have demonstrated by well-designed experiments the importance of pulmonary lymphatics in the causation of pulmonary edema [1] A reversed Bernheim

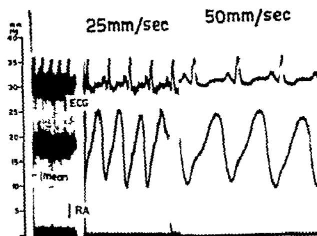


Fig 3 Right atrial pressure tracings showing ventricularization

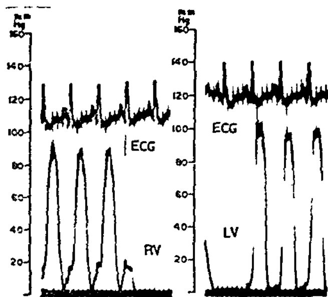


Fig 4 Right and left ventricular pressure (RV and LV) tracings. Note near systemic right ventricular pressures.

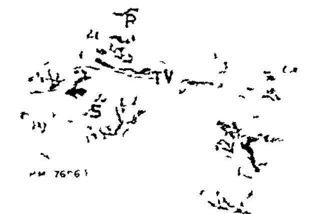


Fig 5 The right ventricle (RV) and the right atrium (RA) have been opened to display the tricuspid valve (TV) and papillary muscles. Arrow points to the ruptured septal (S) papillary muscle

effect was ruled out by the normal LV edp

The physical signs of isolated tricuspid regurgitation in patients with normal right ventricular pressures are pathognomonic However the respiratory variation of the murmur may be difficult to appreciate in a case of severe right ventricular hypertension with a very loud murmur (Grade 5 or 6) A Valsalva maneuver may not show significant changes as noted in the present case

Electrocardiograms may be misleading in some cases of RPM TV A review of the available electrocardiograms of patients reported to have



Fig 6 Histopathologic sections of the lung. A Plexiform lesion B Dilatation lesion. (Hematoxylin-eosin stain magnification ×160)

isolated tricuspid insufficiency by Morgan and Forker showed criteria for left atrial enlargement in about 25% while right atrial enlargement was observed in only one case out of 15 Our case showed features of left and right atrial enlargement These findings along with the history of PND led us to the initial mistaken clinical diagnosis of acute mitral regurgitation Occasionally the chest x ray film may appear normal in normotensive tricuspid regurgitation

It is often said that the hemodynamic consequences of severe tricuspid regurgitation can be well tolerated for long periods Robin and associates have demonstrated long survival of several patients after total removal of the tricuspid valve without prosthetic replacement At least two authors have emphasized that RV edp would be normal or only slightly elevated.

The hemodynamic changes and the natural history of acute tricuspid regurgitation would also be influenced by the underlying cardiac condition. Nearly 50% of patients with RPM TV are dead within 2 weeks and all are either dead or had surgery within 4 months.[1] Our patient lived for 9 months after RPM TV.

Summary

Rupture of a papillary muscle of the tricuspid valve is a rare occurrence and nontraumatic rupture is still rarer. We describe a 26-year-old male with primary pulmonary hypertension presenting with severe dyspnea and paroxysmal nocturnal dyspnea following spontaneous rupture of the septal papillary muscle of the tricuspid valve. The clinical diagnosis was confirmed at autopsy.

REFERENCES

1. Gerry J L Jr, Bulkley B H, and Hutchins G M: Rupture of papillary muscle of the tricuspid valve. A complication of cardiopulmonary resuscitation and a rare cause of tricuspid insufficiency. Am J Cardiol 40:825, 1977.
2. Askey J M: Spontaneous rupture of papillary muscle of the heart. Review with eight additional cases. Am J Med 9:528, 1950.
3. Eisenberg S, and Suyemoto J: Rupture of a papillary muscle of the tricuspid valve following acute myocardial infarction. Circulation 30:588, 1964.
4. Osborn J R, Jones R C, and Jhanke E J Jr: Traumatic tricuspid insufficiency. Haemodynamic data and surgical treatment. Circulation 30:217, 1964.
5. Aleksandrow D, Wysgnacka W, Szezerban J, and Krus S: Traumatic rupture of the right papillary muscle in a patient with congenital atrial septal defect. Am Heart J 69:686, 1965.
6. Ahn A J, and Segal B L: Isolated tricuspid insufficiency. Clinical features, diagnosis and management. Prog Cardiovasc Dis 9:166, 1966.
7. Morgan J R, and Forker A D: Isolated tricuspid insufficiency. Circulation 48:559, 1971.
8. Parmley L F, Manion W C, and Mattingly J W: Non penetrating traumatic injury of the heart. Circulation 18:371, 1958.
9. Collin P, and Daley J J: Tricuspid incompetence complicating acute myocardial infarction. Postgrad Med J 53:51, 1977.
10. Cherian G, Abraham M T, Sukumar I P, Krishnaswami S, and Abraham K A: Idiopathic pulmonary hypertension. A study of 91 patients. VIII World Congr Cardiol 272, 1978.
11. Schlant R G: Altered physiology of the cardiovascular system in heart failure. *In* the Heart, Arteries and Veins, ed 3. Tokyo, 1974, McGraw Hill Kogakusha Ltd., p 427.
12. Unley H W, Leeds S E, Sampson J J, and Friedman M: Right duct lymph flow in experimental heart failure following acute elevation of left atrial pressure. Circ Res 20:306, 1967.
13. Brandenberg R O, McGoon D C, and Campeau L: Traumatic rupture of the chordae tendinae of the tricuspid valve. Successful repair twenty four years later. Am J Cardiol 18:911, 1966.
14. Shabetai R, Adolph R J, and Spencer F C: Successful replacement of the tricuspid valve 10 years after traumatic incompetence. Am J Cardiol 18:911, 1966.
15. Robin E, Thomas N W, Arbulu A, Ganguly S N, and Magnisalis K: Haemodynamic consequences of total removal of the tricuspid valve without prosthetic replacement. Am J Cardiol 35:481, 1975.
16. Jhanke E J, Nelson W P, Aaby G V, and Fitzgibbon G B: Tricuspid insufficiency. The result of non penetrating cardiac trauma. Arch Surg 95:880, 1967.

Bjork-Shiley mitral valvular dehiscence*

Documented by radiography echocardiography fluoroscopy and cineangiography

Patrick K C Chun M D MAJ MC
Sol I Rajfer M D MAJ MC
Dennis J Donohue M D MAJ MC F A C C
Thomas E Bowen M D, LTC, MC
James E Davia M D COL MC F A C C
Washington D C

Radiography echocardiography fluoroscopy and cineangiography are non invasive ways to evaluate dysfunction of prosthetic valves The normal echocardiographic appearance of a Bjork Shiley prosthetic valve has been reported Furthermore two cases with echocardiographic features of Bjork Shiley mitral perivalvular leaks have been reported However only one of these cases had cineangiographic confirmation We report here a case with combined radiographic echocardiographic fluoroscopic as well as cineangiographic findings of prosthetic valvular dehiscence confirmed at surgery

Case report

The patient was a 20 year old black male He presented on September 1 1977 with a three week history of an illness characterized by fever malaise as well as left wrist and right ankle pain He had been treated with oral penicillin prior to his presentation He denied any venereal contact dysuria or pyuria recently He denied further any history of drug abuse heart murmur prior heart disease or rheumatic fever He was admitted to the hospital where physical examination revealed a temperature of 102 4 degrees mild dehydration associated with heat swelling and decreased range of motion of the left wrist and right ankle Petechial lesions of the palms and soles were noted No abnormal cardiovascular findings were noted The patient was felt to have partially treated disseminated gonococcal septicemia He was given high doses of intravenous penicillin with continued temperature spikes However on September 3 1977 the blood joint fluid and urine samples were growing *Staphylococcus aureus* and the antibiotic was changed to methicillin Re examination revealed a new systolic murmur which was initially thought to be benign However over the next 3 days the murmur increased in intensity and was felt to be consistent with mitral insufficiency An *S* sound developed as well An echocardiogram was performed and revealed a normal size left ventricle as well as an enlarged left atrium Vegetations on the mitral valve were also demonstrated

On September 8 1977 a left central facial paresis was noted A cerebral angiogram revealed an obstruction in the right internal carotid artery age undetermined On September 1[illegible] the patient was noted to have an absent right brachial pulse An angiogram revealed obstruction at the axillary brachial region and circumflex-humeral level Embolectomy was performed with a purulent embolus removed He was treated with vancomycin with defervescence of his fever in three days He remained afebrile until September 28 when he again began to spike daily temperatures All blood cultures including fungal cultures were negative to date

On October 7 1977 the patient underwent right and left heart catheterization (Table I *A*) Pulmonary artery pressures were essentially normal Pulmonary capillary wedge pressures showed an A wave of 8 mm Hg and V wave of 11 mm Hg with a mean of 5 mm Hg There was no evidence of a left to right shunt Oxygen saturation studies were normal The cardiac index was noted to be 3 6 liters per minute per square meter determined by thermodilution technique A left ventricular angiogram revealed 2+ mitral regurgitation There was also the finding of a pedunculated abnormality of the anterior mitral leaflet suggestive of a vegetation The left ventricular end diastolic pressure was 8 mm Hg at rest rising to 10 mm Hg post angiography There was no evidence of aortic regurgitation

On October 8 1977 the patient underwent mitral valve

From the Card[illegible] and Th[illegible] Su[illegible] Servi[illegible] Walt[illegible] R[illegible] Army Medic[illegible] Cent[illegible] Wa[illegible] hi[illegible] gton D C

Received f[illegible] publ[illegible] O[illegible] 30 1[illegible]
Accepted f[illegible] Dec 11 19[illegible]

Reprint requests Card[illegible] Servi[illegible] ATTN R[illegible] print Walter Reed Army Medi[illegible] Cente[illegible] W[illegible] hingt[illegible] D C [illegible]012

The op[illegible] ns or asserti[illegible] n[illegible] herein are th[illegible] of the authors and are n[illegible] to be [illegible] n trued [illegible] ffici[illegible] l [illegible] a[illegible] [illegible] the [illegible] iews of the Department of the Army [illegible] th[illegible] Dep[illegible] of Def nse



Fig 1 Chest x ray revealing a markedly tilted ɩalɩe and florid pulmonary edema

Table I Cardiac catheterization data Me ın systolic and diastolic pressures (mm Hg)

	Date of procedure							
Location	*A* *Oct 7 77*		*B* *Oct 21 77*		*C* *Nov 2? 77*		*D* *Dec 11 77*	
Right atrium	a = 6 v = 5	— 5	a = 8 v = 6	— 5	a = 8 v − 4	— 4		
Right ventricle	3?/6		28/6		50/10			
Pulmonary artery	32/8	— 22	26/12	— 20	50/30	— 40	40/24	— 28
Pulmonary capillary wedge	a = 8 v = 11	— 5	a = 14 v = 18	— 14	a − 22 v = 40	— 28	a = 36 v = 40	— 30
Left ventricular end dia tolic pressure	8						16	
Cardiac index (L /min /M)	3 6							

replacement with a No 27 Hancock porcine valve A 2 by 2 cm vegetation was seen on the atrial side of the anterior leaflet of the mitral valve Several small crust like lesions were also located on the mitral valve near the anteromedial commissure Postoperatively the patient developed first degree A V block a pericardial effusion and right peroneal nerve damage

He remained stable until October 21 1977 when he was found to be in acute pulmonary edema Cardiac catheteriza tion (Table I *B*) revealed a trace amount of mitral regurgita tion with normal left and right sided pressures He was treated with diuretics with significant clinical improvement However on repeated examination the patient was found to have physical findings compatible with that of moderate to severe mitral stenosis with progressive pulmonary hyperten sion secondary to a small annular ring which would only accommodate a No ?7 Hancock valve The patient therefore underwent recatheterization on November 22 197? (Table I *C*) *Pressures were noted to be as follows* a pulmonary artery pressure of 50/30 mm Hg with a mean of 40 mm Hg and a pulmonary artery wedge pressure with an A wave of 2? mm Hg and a V wave of 40 mm Hg with a mean of 28 mm Hg. In light of the *progressive rise in pulmonary artery pressures*, the patient underwent mitral valve replacement on November 30 19 7 with a No 27 Bjork Shilev prosthetic valve The patient did well postoperatively

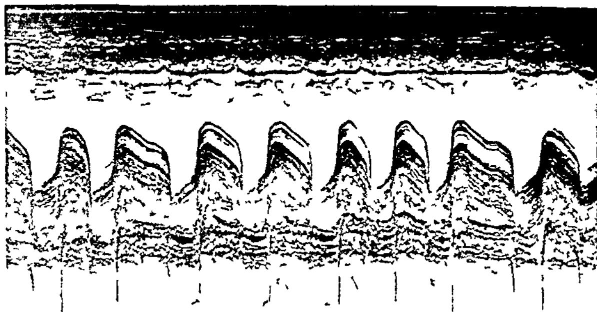


Fig 2 Echocardiogram with a characteristic hump on the anterior leaflet of the mitral valve consistent with frank dehiscence

On the morning of December 11 1977 the patient had acute onset of dyspnea tachycardia and hypotension Physical examination revealed him to be lethargic confused and in shock with rales over the entire lung fields Cardiac examination revealed crisp closing prosthetic clicks There were no murmurs noted His chest x ray revealed a markedly tilted valve and florid pulmonary edema (Fig 1) An electrocardiogram revealed the patient to have a left bundle branch block and first degree heart block unchanged from previous tracings The patient rapidly deteriorated necessitating intubation vasopressors and other measures—i e large doses of furosemide steroids and chest tubes placed bilaterally for drainage A Swan Ganz catheter was inserted and revealed a pulmonary artery diastolic pressure of 36 mm Hg

Emergency portable echocardiogram was performed and revealed a characteristic hump on the prosthetic valve echo *consistent with frank dehiscence of the prosthetic valve* (Fig 2) He was taken to the cardiac catheterization laboratory (Table I D) where the pulmonary capillary wedge mean pressure was 30 mm Hg with an A wave of 36 mm Hg and a V wave of 40 mm Hg The pulmonary artery pressure was 40/?4 mm Hg with a mean of 28 mm Hg The left ventricular end-diastolic pressure was 16 mm Hg Cardiac index was determined to be 1 1 L/min/M by thermodilution technique Fluoroscopy revealed marked tilting of the prosthetic valve with an excursion of 51 degrees suggestive of dehiscence of the prosthesis (Fig 3) A left ventricular angiogram revealed 4+ mitral regurgitation (Fig 4) The patient was immediately taken to surgery where the valve in the annulus was noted to be supported by only three sutures while the other 10 sutures had pulled through The valve was also noted to be prolapsing into the left atrium The valve was removed and was replaced with a new No 27 Bjork Shiley mitral valve Postoperatively the patient became septic and died on January ? 1978

Discussion

Evaluation of prosthetic valve function requires strict attention to detail and frequent serial examinations Changes on auscultation x rays echocardiography and other non invasive examinations are evident only with repeated evaluation [1] Valvular dysfunction may vary from obstruction to frank valvular dehiscence and massive regurgitation as in our patient The dehiscence of the sewing ring due to suture breakage or disruption from the sewing bed because of friable calcific or necrotic tissue is a major cause of dysfunction It is helpful to be familiar with the particular valve and its difficulties in order to arrive at an expeditious diagnosis of the nature of the malfunction This patient presented with a sudden calamity The mode and time of presentation of his valvular dysfunction was a major aid in arriving at the diagnosis During his dramatic deterioration the patient manifested normal prosthetic sounds and the absence of a murmur in spite of severe paravalvular leakage

The x ray revealed the patient to be in florid pulmonary edema and to have exaggerated tilting



Fig 3 A and B Fluoroscopic documentation of marked tilting of the valve with an excursion of 51 degrees suggesting dehiscence

of his valve Cinefluoroscopy was valuable in detecting excessive cyclic excursion of the sewing ring strongly suggestive of valvular dehiscence 4+ mitral regurgitation was noted around the sewing ring

The detachment of the valve prosthesis is caused by the breaking and loosening of sutures from the sewing bed This was brought about probably by the strain in the sutures in the anchoring tissue resulting from the force of the ventricular contraction In the mitral position the normal movement of the prosthesis is anterior and posterior along its long axis and side to side on its vertical axis The strain on the suture line is greatest at the medial and lateral aspects of the sewing ring If the suture breaks in one of these locations as in our patient it puts a strain on the adjacent sutures causing progressive dehiscence and may lead to complete detachment and embolization of the entire prosthetic valve

The prosthetic detachment was diagnosed unequivocally by roentgenographic techniques Plain x ray of the chest suggested detachment by the abnormal orientation of the prosthesis The detachment was more evident by fluoroscopy A to and fro motion of the partially detached valve was seen and the axis at the base of the prosthesis changed during ventricular contraction and relaxation Cinefluoroscopy permitted easy measurement of this tilting motion The foregoing constituted a positive method of demonstrating the prosthetic valve detachment

Studies using the echocardiogram in the diagnosis of prosthetic valve dysfunction are now becoming more frequent Correlation of the echocardiogram with radiography fluoroscopy and angiography have defined the movement patterns for normally functioning prosthetic valves Other reports have shown malfunction characterized by disc motion disc excursion and relation of the disc and cage motions to other cardiac events In particular disc motion of the Bjork Shiley prosthetic valve can be readily assessed by echocardiography Because of the asymmetry of the valve proper disc and echo transducer alignment are necessary for optimal detection of disc excursion According to Douglas and Williams[1] when the ultrasound beam is perpendicular to the maximally open disc such an alignment usually is most readily achieved Patients who undergo



Fig 4 A left ventricular angiogram revealing 4+ mitral regurgitation

prosthetic valve replacement should have an initial prosthetic echogram accomplished postoperatively as soon as technically feasible

Although contrast angiography is the most sensitive indicator of prosthetic valvular detachment radiography echocardiography fluoroscopy and cineradiography should be used in all suspected cases Serial studies with the foregoing non invasive procedures beginning with an early postoperative control study are recommended

Summary

This case report presents combined radiographic echocardiographic fluoroscopic and cineangiographic findings of the dehiscence of a Bjork Shiley mitral prosthetic valve The valvular dehiscence was confirmed at surgery A distinct rounding of the opening phase of the valve was recorded on the echocardiogram Other clinical evidence documenting the severe valvular dehiscence is reported in detail Non invasive procedures are therefore invaluable in recording prosthetic valvular dysfunction

REFERENCES

1 Douglas J E and William G D Echocardiographic evaluation of the Bjork Shiley prosthetic valve Circulation 50 52 1974
2 Bernal Ramirez J A and Phillip J H Echocardiographic study of malfunction of the Bjork Shiley prosthetic heart valve in the mitral position Am J Cardiol 40 449 1977
3 Hipona F A Lerona P T and Paredes S Radiologic diagnosis of late complication associated with cardiac valve surgery in acquired heart disease Radiol Clin North Am IX 265 265 1971
4 Kloster F E Diagnosis and Management of Complications of prosthetic heart valves Am J Cardiol 35 8 2, 1975
5 Hildner F J Detection of prosthetic valve dysfunction by bedside and laboratory evaluation Cardiovasc Clin 5 290 1973
6 White A F Dinsmore R E, and Buckley M J Cineradiographic evaluation of prosthetic cardiac valves, Circulation 48 882 1973
7 Burch G E and Giles T D Clinical evaluation of aortic and mitral valve prostheses AM HEART J 92 245 1976
8 Fishman N H Hutchinson J C and Roe B B Prevention of prosthetic cardiac valve detachment, Surgery 67 867 1970

Clinical pathologic conference

Left and right ventricular myocardial infarction in idiopathic dilated cardiomyopathy

Jeffrey M Isner MD
Renu Virmani MD
Samuel B Itscoitz MD
William C Roberts MD
Bethesda and Takoma Park Md

DR ROBERTS Dr Isner will present the *patient s story* and *clinical findings*

DR ISNER N S (Washington Adventist Hospital No 14403 1) was a 62 year old woman who died on September 23 1978 Since age 53 years (1969) she had known of a heart murmur and a large heart She was asymptomatic until age 60 years when she developed exertional dyspnea and pedal edema Examination then revealed distended neck veins basilar pulmonary rales a large heart S and S sounds an apical holosystolic murmur and another systolic murmur which increased with inspiration at the left sternal border The liver was palpable and both legs were edematous Electrocardiogram disclosed sinus tachycardia with non specific ST T wave changes The patient was started on digoxin and diuretics She was hospitalized twice during the subsequent 2 years for overt congestive heart failure Ten months before death an echocardiogram disclosed a dilated poorly contracting left ventricle

Because of increasing congestive cardiac failure she was hospitalized 5 days before death She denied ever having chest pain She had drunk alcohol infrequently and never had hypertension to her knowledge Her blood pressure on admission was 110/90 mm Hg with a pulsus paradoxus of 20 mm Hg Despite distention above the sternal angle of the neck veins the lung fields were clear The right ventricular impulse was more prominent than the left ventricular impulse The remainder of the precordial examination was unchanged from the findings described 2 years earlier The liver was enlarged and severe (4+/4+) subcutaneous edema was present in the lower legs The hematocrit was 35 per cent fasting serum glucose 109 mg/dl serum total cholesterol 170 mg/dl serum glutamic oxalo acetic transaminase 61 mU/ml (normal 7 to 40) lactic dehydrogenase 302 mU/ml (normal 100 to 225) creatinine phosphokinase 208 mU/ml (normal <145) with cardiac (MB) fraction 1 9 (nl ≤ 3 per cent) The electrocardiogram (Fig 1) showed a vertical axis and inverted T waves in Leads III and aV_F the chest radiograph (Fig 2) showed marked cardiomegaly and the echocardiogram (Fig 3) was similar to the one recorded 10 months earlier Her course worsened On the day of death her skin cooled and became moist the blood pressure fell and the electrocardiogram (Fig 1) showed left bundle branch block With ambu bag pulmonary assistance the arterial pO was 69 mm Hg pCO 55 mm Hg and pH 7 12 (On admission when breathing room air the pO had been 85 mm Hg pCO 31 mm Hg and pH 7 45) The patient was intubated and a Swan Ganz catheter was inserted Initial pressures (in mm Hg) were right atrial mean 24 right ventricle 55/24 pulmonary artery 55/35 and mean pulmonary capillary wedge 25 Despite intravenous administration of saline and dopamine the systemic blood pressure continued to fall Subxiphoid insertion of a needle ruled out cardiac tamponade Shortly thereafter fatal ventricular fibrillation occured

From the Pathology Branch National Heart Lung and Blood Institute National Institutes of Health Bethesda Maryland, and the Department of Cardiology Washington Adventist Hospital Takoma Park Maryland

Received for publication on Dec 29 19 8

Reprint requests William C Roberts MD Building 10A, Room 3E30 National Institutes of Health, Bethesda Md 20014

0002 8703/80/080235 + 08$00 80/0

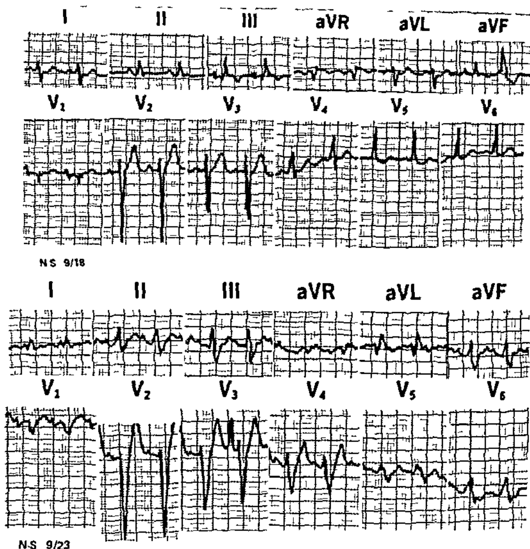


Fig 1 Electrocardiograms On admission (9/18) 5 days before death the T wave inversions in Leads III and aV are the only findings consistent with a scar in the posterior left ventricular free wall Left bundle branch block appeared on the day of death (9/23)

DR ROBERTS Dr Virmani would you decribe the *findings at necropsy*

DR VIRMANI At necropsy (WAH No A7867) about 100 ml of serous fluid was present in the pericardial sac The heart weighed 580 grams All four chambers were markedly dilated There was transmural scarring of the posterior walls of both left and right ventricles and of the adjacent ventricular septum (Figs 4 and 5) There were no foci of myocardial necrosis Thrombi were present in both ventricles and in the right atrial appendage The major epicardial coronary arteries were wide open (Fig 6) At no point were any portions of any epicardial coronary artery >25 per cent narrowed in cross sectional area The lungs together weighed 900 grams Two hemorrhagic infarcts were present one in the lower lobe of the left lung and the other in the upper lobe of the right lung Some adjacent pulmonary arteries contained thromboemboli Small healed infarcts were present in each kidney The liver weighed 1 450 grams and was congested

DR ROBERTS Thus we have a patient who was known to have cardiomegaly and an abnormal electrocardiogram for at least 10 years, evidence of chronic congestive heart failure for at least 2 years never evidence of chest pain and at necropsy very dilated ventricular cavities containing thrombi large transmural scars involving the free walls of both left and right ventricles and the ventricular septum and widely patent virtually normal epicardial coronary arteries *Dr*

Itscoitz what was your *clinical diagnosis* in this patient?

Dr Itscoitz Three possibilities were considered One was coronary heart disease particularly in view of her age (62 years) Against this diagnosis however was the absence of chest pain electrocardiographic absence of clear myocardial damage and the absence of risk factors for atherosclerosis Her total serum cholesterol was 170 mg/dl she did not smoke her blood pressure had always been normal and her fasting blood sugar was normal Idiopathic dilated cardiomyopathy was favored by the history of chronic congestive heart failure the marked cardiomegaly and the absence of chest pain or clear evidence of organic valve disease The third diagnosis considered was pericardial heart disease This possibility was considered because of the extremely large cardiac silhouette by chest radiograph the extreme prominence of features of right sided congestive failure (the neck veins were enormously distended while the lung fields were clear and she was able to lie flat in bed without distress) and the occurrence of diastolic pressures in the right ventricle and main pulmonary arteries similar to the mean pressures in the right atrium and pulmonary arterial wedge position The possibility of cardiac tamponade was so high immediately before death that a needle was inserted into the pericardial sac but fluid was not detected

Dr Roberts Dr Virmani your necropsy observations in this patient are consistent with idiopathic dilated cardiomyopathy What *morphologic criteria make this diagnosis at necropsy?*

Dr Virmani To diagnose idiopathic dilated cardiomyopathy at necropsy five criteria must be met (1) both ventricular cavities must be dilated (2) the heart weight must be increased (> 350 gms in adult women and > 400 gms in adult men) (3) the lumens of the major epicardial coronary arteries must be < 75 per cent narrowed in cross sectional area by atherosclerotic plaque (4) the four cardiac valves must be anatomically normal or have only minimal focal small scars and (5) no associated systemic or other known cardiovascular conditions can be present In addition intracardiac thrombi are usually present in one or more cardiac cavities but this finding is not essential for diagnosis

Dr Roberts Dr Itscoitz although many clinical definitions of idiopathic dilated cardiomyopathy include the absence of systemic hypertension and the absence of valvular heart disease many of these patients have systemic hypertension and most before the end have one or more precordial murmurs *How do you diagnose idiopathic dilated cardiomyopathy in the presence of systemic hypertension or precordial murmurs or both?*



Fig 2 Posteroanterior chest radiograph on admission 5 days before death. The cardiac silhouette is markedly enlarged and the pulmonary vessels are prominent—i e "congested"

Dr Itscoitz If systemic hypertension is present throughout the entire clinical course I do not believe the diagnosis of idiopathic dilated cardiomyopathy would then be appropriate If systemic hypertension were present however only at the beginning of the patient s course and was absent in the last few months the diagnosis of idiopathic dilated cardiomyopathy could still be proper In other words if the blood pressure rises progressively and persists throughout the course diagnosis of idiopathic dilated cardiomyopathy would not be appropriate

In general precordial murmurs appear relatively late in the course and the murmurs may get louder as the ventricular cavities get bigger In the present patient however a precordial murmur preceded the presence of overt congestive heart failure but that is unusual

Dr Roberts An unusual feature of this

Fig 3 Echophonocardiograms recorded one day before death. *Left* ventricular dilatation with diminished excursion of both septum (*IVS*) and left ventricular (*LV*) free wall. There is no evidence of pericardial effusion. *PV* = right ventricle *AML* and *PML* = anterior and posterior mitral leaflets respectively. *Middle* Severely dilated right ventricular outflow tract (*RVOT*) *Ao* = aortic valve within aorta *LA* = left atrium *SM* = systolic murmur *Right* Another view of the markedly dilated right ventricle at the level of the tricuspid valve (*TV*)

patient morphologically was the presence of a very large cardiac scar involving not only the left ventricular free wall and ventricular septum but also the right ventricular free wall I have studied the hearts of 153 necropsy patients with idiopathic dilated cardiomyopathy and this patient had the largest ventricular scar of any In addition this is one of the few patients with idiopathic dilated cardiomyopathy seen personally at necropsy with extensive right ventricular scarring Dr Virmani *could you enlighten us to the cause of ventricular scarring in patients with idiopathic dilated cardiomyopathy*

DR. VIRMANI The cause of cardiac ventricular scarring in patients with idiopathic dilated cardiomyopathy is unclear By definition the epicardial coronary arteries cannot be significantly narrowed in this condition and therefore narrowing of these vessels is not a cause of the scarring Embolism to the coronary arteries from thrombi located within the left side of the heart is a potential cause of left ventricular scarring In patients with coronary embolism however whom we have studied at necropsy there usually is evidence of occlusion of one or more of the intramural coronary arteries [1] Multiple histologic sections of the ventricular walls in the present patient however disclosed no abnormality of the intramural coronary arteries and that observation is strong evidence against embolism as a cause of scarring The extremely diminished cardiac output which occurs in patients with idiopathic dilated cardiomyopathy generally leads to a "global" myocardial ischemia and not so much to a focal myocardial ischemia Ventricular scarring is always focal and therefore its explanation in these patients is uncertain

DR ROBERTS Recently Dr Isner and I reviewed a large number of necropsy patients with coronary heart disease who had both right ventricular and left ventricular myocardial infarction The present patient however shows that right ventricular infarction may occur in the absence of coronary arterial luminal narrowing. Dr Isner *what features allow the clinical diagnosis of right ventricular infarction?*

DR. ISNER From review of clinical and necropsy features of 33 patients with right ventricular myocardial infarction associated with left ventricular infarction three findings suggest clinical

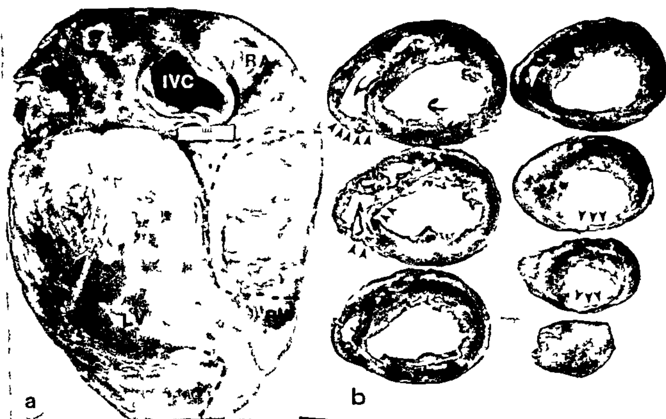


Fig 4 a and b Transmural ventricular scarring in the patient described *a* Posterior view of heart showing external appearance of left ventricular (*LV*) and right ventricular (*RV*) scars (*enclosed by dashed lines*) *b* Transverse sections of ventricles from base (*upper left*) to apex (*lower right*) *The arrows* designate sites of transmural scarring *LA* = left atrium *RA* = right atrium *IVC* = inferior vena cava

ly the presence of right ventricular infarction (1) electrocardiographic evidence of an inferior or posterior left ventricular wall myocardial infarction (2) evidence of right ventricular dilatation and (3) a right ventricular filling pressure equal to or out of proportion to the left ventricular filling pressure *Of our 33 patients all had an associated* infarction of the posterior (inferior) wall of the left ventricle In contrast of 97 patients with isolated anterior wall infarction of the left ventricle none had associated right ventricular myocardial infraction Furthermore among the patients with posterior wall left ventricular infarcts those with right ventricular myocardial infarcts had right ventricular dilatation observed at necropsy nearly three times more frequently than did the patients without right ventricular myocardial infarcts Comparison of patients with right ventricular myocardial infarction however disclosed no differences in the patient s age sex extent of coronary arterial luminal narrowing presence of right ventricular hypertrophy or right ventricular thrombi or the length of symptoms of myocardial ischemia

Dr Roberts Dr Isner *what clinical features in the present patient* in retrospect *might have suggested the presence of healed right ventricular infarction?*

Dr Isner First as Dr Itscoitz pointed out the signs of right ventricular failure were out of proportion to those of left ventricular failure The neck veins were severely distended and yet the patient could lie flat in bed without respiratory distress Secondly echocardiograms done at 10 months and at one day before death both demonstrated severe right ventricular dilatation a finding at least consistent with right ventricular myocardial infarction Surprisingly no electrocardiographic evidence of unequivocal infarction *of the posterior wall of the left ventricle* however

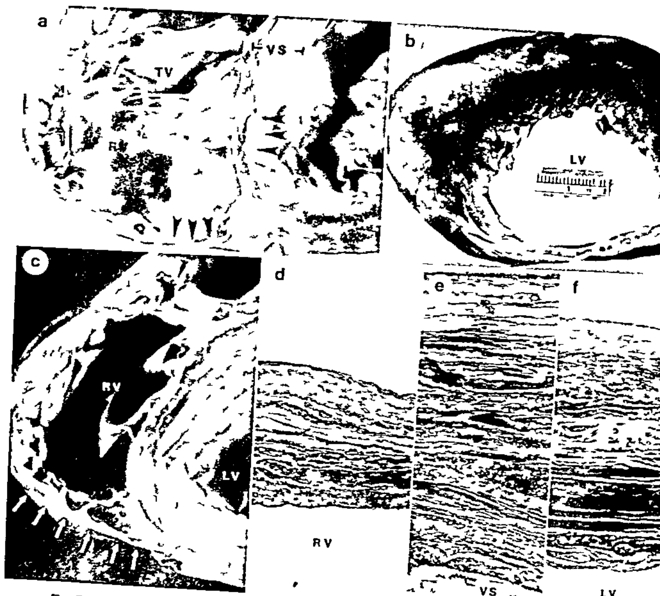


Fig 5 a through f Transmural ventricular scarring *a* *Arrows* designate thinning due to healed myocardial infarct of ventricular septum (*VS*) and posterior wall of ventricle (*RV*) *TV* = tricuspid valve *b* Posterior wall of left ventricle (*LV*) which is scarred and thinned. *c* Posterior right ventricular scar (*arrows*) at level approximately 1 cm caudad to *a* *d* *e* *f* Photomicrographs of healed transmural infarcts of RV VS and LV respectively (Movat stains each original magnification ×36)

was present The elevation of the pulmonary arterial diastolic pressure to a level of 9 mm Hg greater than the mean pulmonary capillary "wedge pressure was a reflection of pulmonary arterial hypertension in this patient the result of pulmonary emboli The elevation of right ventricular end-diastolic pressure however was out of proportion to both the elevated left ventricular end diastolic pressure *and* the degree of pulmonary hypertension resulting from the pulmonary emboli The degree of elevation of right ventricular end-diastolic pressure in this patient would be consistent with an associated right ventricular myocardial infarction

DR. ROBERTS Dr Isner you and others have mentioned that the signs of right ventricular infarction may mimic those of cardiac constriction or cardiac tamponade How do you *distinguish the signs emanating from right ventricular infarction from those of pericardial heart disease?*

DR. ISNER First electrocardiographic or enzymatic evidence of myocardial infarction certainly would increase suspicion of an associated right

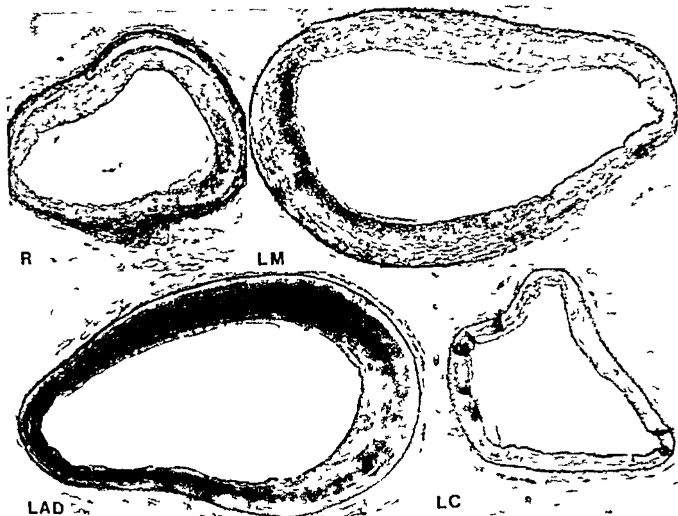


Fig 6 Photomicrographs of each of the four major (right [*R*], left main [*LM*], left anterior descending [*LAD*], and left circumflex [*LC*]) coronary arteries at sites of maximal luminal narrowing None of the coronary arteries were narrowed > 25 per cent in cross sectional area (Movat stain each original magnification ×24)

ventricular infarction as opposed to primary pericardial disease Secondly right ventricular dilatation would be most unusual in a patient with impaired cardiac filling due to pericardial heart disease whereas right ventricular dilatation is commonly present in patients with right ventricular myocardial infarcts Finally differentiation between pericardial heart disease and right ventricular myocardial infarction may not be possible on the basis of physical examination alone and the use of noninvasive tools such as echocardiography and radionuclide angiography or invasive studies may be necessary to determine whether the clinical appearance of the patient is due to pericardial heart disease or to right ventricular myocardial infarction associated with left ventricular infarction

DR. ROBERTS The majority of patients with idiopathic dilated cardiomyopathy have mural thrombi in one or more ventricular cavities The most frequent site is the left ventricle next the right ventricle third the right atrial appendage and fourth the left atrial appendage The exact cause of these intracardiac thrombi is unclear but it seems most reasonable to believe that they result simply from relative blood stasis or inadequate chamber emptying The danger of intracardiac thrombi obviously is that they are sources of systemic and pulmonary emboli In the present patient emboli were observed at necropsy in both

renal and pulmonary arteries with resulting infarcts of each organ Dr Isner in retrospect *what features suggested pulmonary embolism as the* terminal *event in our patient?*

DR ISNER The acute drop in blood pressure in spite of longstanding congestive heart failure the drop in systemic arterial oxygen content and the appearance of left bundle branch block suggested this possibility

REFERENCES

1 Roberts W C Coronary embolism a review of causes consequences and diagnostic considerations Cardiovasc Med 3 699 1978

2 Isner J M and Roberts W C Right ventricular infarction complicating left ventricular infarction secondary to coronary heart disease Frequency location associated findings and significance from analysis of 236 necropsy patients with acute or healed myocardial infarction Am J Cardiol 42 885 1978

3 Lorell B Leinbach R C Pohost G M Gold H K Dinsmore R E Hutter A M Pastore J O, and De Sanctis R W Right ventricular infarction Clinical diagnosis and differentiation from cardiac tamponade and pericardial constriction, Am J Cardiol 43 465 1979

4 Jensen D P Goolsby J P and Oliva P B Hemodynamic pattern resembling pericardial constriction after acute inferior myocardial infarction with right ventricular infarction Am J Cardiol 42 858 1978

5 Roberts W C and Ferrans V J Pathologic anatomy of the cardiomyopathies Idiopathic dilated and hypertrophic types infiltrative types and endomyocardial disease with and without eosinophilia Hum Pathol 6 287 1975

6 Lynch R E Stein P D and Bruce T A Leftward shift of frontal plane QRS axis as a frequent manifestation of acute pulmonary embolism Chest 61 443 1972

Prevention of cardiogenic shock

J S Geddes M D
A. A J Adgey M D
J F Pantridge M D
Belfast Northern Ireland

Cardiogenic shock occurs in 10% to 15% of hospitalized patients with acute myocardial infarction[1] It is usually related to massive destruction of the myocardium In a few patients the direct cause is a sudden structural catastrophe such as papillary muscle rupture or septal perforation Among those who die from cardiogenic shock the amount of left ventricular myocardium infarcted varies from 35% to 70%[3]

Since shock is associated with massive myocardial infarction therapeutic interventions have been unrewarding despite intra aortic balloon counter pulsation and coronary revascularization with or without additional surgery

That appropriate early intervention might limit myocardial damage and prevent cardiogenic shock was suggested nearly 10 years ago It was found that when therapy was initiated within 3 hours of the onset of myocardial infarction the incidence of cardiogenic shock was 4% and when therapy was delayed longer than 3 hours the incidence was 13%

Extensive loss of myocardium responsible for cardiogenic shock occurs in a stepwise fashion[1,3] Extension of recent infarction occurs in close temporal proximity to the clinical onset of shock

It has been observed that every patient dying with cardiogenic shock had damage to the ventricular apex and that 84% of such patients had severe disease of the left anterior descending coronary artery It is of interest that patients dying from left ventricular failure following myocardial infarction show extensive myocardial damage similar to that of patients dying from cardiogenic shock[7]

Pathogenesis of extension of infarction

That the ultimate magnitude of the infarct may be influenced by factors operating after coronary occlusion has been confirmed in the animal laboratory Clinical evidence supports the proposition that progressive myocardial damage may occur in patients who later develop shock[0] Progressive destruction of myocardium following coronary occlusion is readily explicable Dysrhythmias and autonomic disturbance immediately after the onset of coronary occlusion may alter unfavorably the balance between oxygen supply and demand at the periphery of the infarct Aggravation of left ventricular dysfunction is likely to result This predisposes to an increase in left ventricular filling pressure or a reduction in arterial pressure or both There may be a compensatory increase in heart rate Any combination of these changes will have further detrimental effects on jeopardized myocardium Thus there may be a vicious cycle involving continuing extension of the infarct and impairment of left ventricular function

In the prevention of progressive myocardial damage the time at which therapy is initiated is crucial. In the dog irrecoverable damage to the myocardium commences about 20 minutes after the onset of ischemia Reperfusion studies indicate that about 3̄5% of the tissue destined to[3] undergo necrosis is already beyond recovery 40 minutes after coronary occlusion and that when 6 hours have elapsed the percentage has increased to 90[2] If the results of these animal experiments

From The Northern Ireland Regional Medical Cardiology Centre Royal Victoria Hospital, Belfast, Northern Ireland

Received for publication May 21 1979

Reprint requests Dr J F Pantridge Director Regional Medical Cardiology Centre Royal Victoria Hospital Belfast BT1 6BA Northern Ireland.

000?-8703/80/0?0?43 + 12$01.20/0

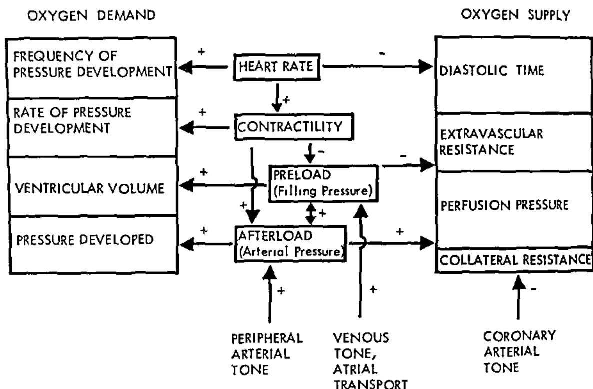


Fig 1 Factors influencing myocardial oxygen economy Interactions positive or negative between the factors are indicated by arrows Because of these interactions the net effect of an intervention cannot always be predicted (From Pantridge J F The Acute Coronary Attack Grune & Stratton Inc 1975 New York and Pitman Medical Tunbridge Wells England Reproduced by permission)

are applicable to clinical myocardial infarction interventions initiated later than one hour after the onset of the coronary attack are likely to be of limited value in the prevention of infarct extension and the longer the delay the less will be the effect of therapy

The quantity and precise geometry of myocardium which is critically ischemic at any one time following coronary occlusion is unknown Nevertheless, the demonstration that death of perhaps half of the ischemic tissue takes place during the 5 hour period after the end of the initial 40 minutes of ischemia indicates clearly that a potential for modifying importantly the magnitude of the infarct exists Where a mobile coronary care unit is available one half of the patients can be treated within 1 hour 40 minutes after the onset of symptoms In places where prehospital coronary care is available limitation of the mass of myocardium destroyed is a practical proposition

Oxygen economy of ischemic myocardium

While the object of early intervention is to obtain the most favorable balance between work and useful pressure the simultaneous reduction of myocardial work and increase in perfusion pressure derived from cardiac contraction is rarely achieved The factors affecting myocardial oxygen economy are summarized in Fig 1 Ischemic myocardium performs relatively little work but experimental evidence indicates that increasing myocardial work is harmful directly or indirectly to jeopardized myocardium[8] Myocardial oxygen requirement depends on heart rate the inotropic state and tension development (which in turn is dependent on developed pressure and the volume of the left ventricle in early systole according to the Laplace law)[14,15] Coronary blood flow is affected by arterial pressure left ventricular diastolic pressure (which when elevated limits flow to the endocardium) diastolic time and coronary vascular tone[18,19] Coronary flow is severely restricted when the mean arterial pressure falls below 70 mm Hg[10] Peripheral as well as central hemodynamics may be disturbed following myocardial infarction[2,22]

It is clear that tachycardia hypotension left ventricular defeat and inappropriate increase in myocardial contractility which may result from

catecholamine secretion will be harmful in the presence of ischemia The effects of bradycardia will also be deleterious if a slow heart rate results in hypotension Hypertension might be expected to be beneficial since the resultant increase in coronary flow might exceed the increase in myocardial oxygen requirement[21] Induced hypertension has indeed been shown to have salutary effects in the presence of experimental coronary artery stenosis[24] Nevertheless there is evidence that the correction of hypertension has salutary effects on ischemic myocardium in patients with myocardial infarction[5] It is likely that in the usual clinical situation an increase in left ventricular diastolic pressure which may be associated with hypertension combines with the increase in developed pressure to negate the benefit resulting from the improvement in coronary perfusion pressure In addition, hypoxic myocardium contracts poorly against a high resistance

The role of coronary vascular resistance and in particular collateral resistance in determining the magnitude of the infarct is difficult to evaluate Spasm at sites of organic arterial disease has been reported to occur commonly in clinical infarction Agents affecting vascular resistance in the region of the ischemic zone inevitably also affect the peripheral vessels and left ventricular filling pressure Nitroglycerin has been shown to have a dilating effect upon coronary collateral vessels in man

At a time when myocardial reserve has been impaired by the development of ischemia any additional myocardial work or reduction in arterial pressure to hypotensive levels resulting from inappropriate constriction or dilatation of peripheral vessels is likely to be harmful Not only may the systemic vascular resistance be abnormal but changes in venous tone may reduce or increase venous return to the heart An inappropriately low filling pressure or an acute reduction in preload appears to predispose to the development of the bradycardia hypotension syndrome[9, 1] Venoconstriction will result in left ventricular failure disproportionate to the degree of reduction in ventricular performance This situation is not infrequently seen during the course of hemodynamic investigations Venoconstriction may persist for as long as 5 days after infarction

The mechanical properties of the ischemic myocardium alter during the hours following coronary occlusion The infarcting tissues swell and become stiff[33, 34] The swelling causes compression of the vessels supplying jeopardized myocardium and may cause extension of the infarct in the absence of other adverse hemodynamic changes Stiffening is associated with stretching the ischemic region assumes larger dimensions but becomes less distensible The paradoxical pulsation evident immediately after experimental coronary occlusion is then reduced[3] The remaining myocardium therefore works more effectively as a pump but any overall increase in ventricular volume resulting from stretching of the ischemic zone will increase oxygen requirements

Ischemic myocardium which is still mechanically active produces a sustained contraction since relaxation is delayed[3] This loss of synchronous activity reduces the mechanical efficiency of the ventricle and compresses the intramural vessels early in diastole when coronary perfusion pressure is maximal

Clinical approach to the salvage of ischemic myocardium

The simple measures that have been employed to limit infarct size involve immediate correction of dysrhythmias correction of the autonomic disturbance and management of clinically apparent hemodynamic abnormalities[1] Relief of pain and anxiety will contribute to the correction of autonomic disturbance and by reducing restlessness will decrease cardiac work The peripheral redistribution of blood resulting from the administration of diamorphine or its analogues will also have salutary effects if the left ventricular filling pressure is elevated

Autonomic disturbance is common at the onset of infarction Among patients seen within 30 minutes only 17% will have a normal heart rate and normal blood pressure Sympathetic overactivity with tachycardia or transient hypertension or both will be evident among one third Parasympathetic overactivity with bradycardia hypotension or both will be evident in approximately 50%[3]

Bradycardia should have a salutary effect since it will be associated with a reduction in oxygen demand Unfortunately among patients with bradycardia seen immediately after the onset of infarction 78% will show associated hypotension with a systolic blood pressure not greater than 100 mm Hg In many of these patients the mean

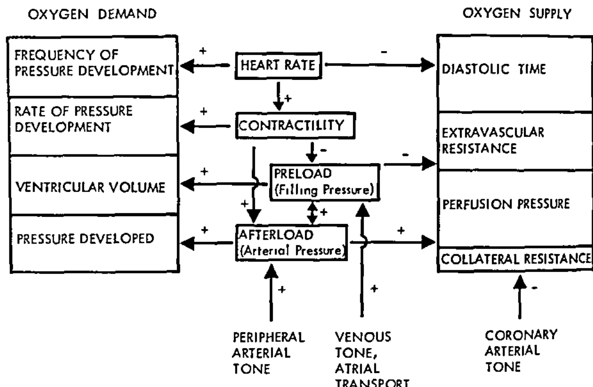


Fig 1 Factors influencing myocardial oxygen economy Interactions positive or negative between the factors are indicated by arrows Because of these interactions the net effect of an intervention cannot always be predicted. (From Pantridge J F The Acute Coronary Attack, Grune & Stratton Inc 1975 New York, and Pitman Medical, Tunbridge Wells England Reproduced by permission)

are applicable to clinical myocardial infarction interventions initiated later than one hour after the onset of the coronary attack are likely to be of limited value in the prevention of infarct extension and the longer the delay the less will be the effect of therapy

The quantity and precise geometry of myocardium which is critically ischemic at any one time following coronary occlusion is unknown Nevertheless, the demonstration that death of perhaps half of the ischemic tissue takes place during the 5 hour period after the end of the initial 40 minutes of ischemia indicates clearly that a potential for modifying importantly the magnitude of the infarct exists Where a mobile coronary care unit is available one half of the patients can be treated within 1 hour 40 minutes after the onset of symptoms In places where prehospital coronary care is available limitation of the mass of myocardium destroyed is a practical proposition

Oxygen economy of ischemic myocardium

While the object of early intervention is to obtain the most favorable balance between work and useful pressure the simultaneous reduction of myocardial work and increase in perfusion pressure derived from cardiac contraction is rarely achieved The factors affecting myocardial oxygen economy are summarized in Fig 1 Ischemic myocardium performs relatively little work but experimental evidence indicates that increasing myocardial work is harmful directly or indirectly to jeopardized myocardium Myocardial oxygen requirement depends on heart rate the inotropic state and tension development (which in turn is dependent on developed pressure and the volume of the left ventricle in early systole according to the Laplace law)[14,15] Coronary blood flow is affected by arterial pressure left ventricular diastolic pressure (which when elevated limits flow to the endocardium) diastolic time and coronary vascular tone[16] Coronary flow is severely restricted when the mean arterial pressure falls below 70 mm Hg[1] Peripheral as well as central hemodynamics may be disturbed following myocardial infarction [22]

It is clear that tachycardia hypotension left ventricular defeat and inappropriate increase in myocardial contractility which may result from

increasing collateral blood flow or the rate of diffusion of substrates and metabolites through ischemic tissue the stabilization of ischemic cells the provision of metabolic support and improvement in arterial oxygenation No attempt will be made to enumerate completely the multitude of techniques so far devised

The difficulties in establishing the efficacy of a given therapeutic regime lie in the caution required in the application of the results of animal experiments to the clinical situation and in the problems of measuring the effects of the intervention on clinical myocardial infarction In addition the wide variation in experimental results must be interpreted in the light of the time after coronary occlusion at which therapy was initiated It is also important to define clearly the clinical situations in which each therapeutic regime is likely to be salutary For example experimental elevation of the arterial pressure may be salutary in the absence of left ventricular failure but detrimental when ventricular function is poor and the effects of digitalis on ischemic myocardium are the reverse of those of raising the arterial pressure in both these situations [illegible]

Monitoring the effects of interventions The possibility of detecting changes in the intensity of ischemia in clinical myocardial infarction has received much attention in recent years Only non invasive methods are suitable for the assessment of the effects of therapy on large numbers of patients Since myocardial function is closely related to intensity of ischemia it is possible that two-dimensional echocardiographic and radionuclide imaging techniques for monitoring regional myocardial contraction will in the future contribute to the assessment of the results of interventions Difficulties in the use of such methods are likely since the effects of treatment will have to be interpreted against the background of rapidly evolving mechanical properties of the ischemic zone Factors such as arterial pressure may affect contraction independently of local ischemia

At present the emphasis is on enzymatic and electrocardiographic techniques

Creatine kinase release The quantity of the enzyme creatine kinase which appears in the peripheral blood following release from moribund cells is regarded as a parameter of the magnitude of the infarct [illegible] A modification of the method of Shell Sobel and co-workers devised by Norris and co-workers [illegible] has been used in a number of investigations The modification involves calculation of the disappearance rate of the enzyme for each patient This calculation may be subject to inaccuracies [illegible] and the use of an average disappearance rate is still preferred by some workers Plasma levels of the enzyme are corrected, cumulatively for estimated loss The accuracy of the method is impaired if the patient is given intramuscular injections which result in enzyme release from skeletal muscle This difficulty may be circumvented if the MB fraction of the enzyme is measured since this fraction is specific for the myocardium. [illegible]

Attempts have been made to predict the remainder of the release curve from the points obtained during the few hours after the onset of enzyme release [illegible] This curve may then be compared with that obtained following therapy A reduction in enzyme release in comparison with that expected would suggest that the effects of therapy have been salutary [illegible] A major disadvantage of this approach is that therapy must be withheld for some hours while the early blood samples are obtained Unfortunately after such delay the possibility of limiting infarct size is minimal

The enzymatic method has another important limitation The removal of creatine kinase from the circulation is largely independent of the hemodynamic situation [illegible] However the fraction of the enzyme which appears in the peripheral blood usually about 30% is inversely related to the interval between the release into the interstitial fluid and passage through lymphatics into the blood stream. An improvement in blood supply to the ischemic region may increase the rate of flow of interstitial fluid into the lymphatics and hence the proportion of the enzyme released which appears in the peripheral blood. An erroneous impression that ischemia had been intensified might result [illegible]

ST segment elevation Measurements of the magnitude of ST segment elevation recorded from multiple leads on the precordium give some indication of the instantaneous intensity of ischemia affecting the underlying myocardium [illegible] A reduction in ischemia will usually result in a lowering of the ST segments and an increase will have the reverse effect Unfortunately interventions which influence ischemia such as variations in heart rate or sympathetic activi

ty may also have direct effects on the action potentials in both ischemic and non ischemic regions Changes in action potential morphology may alter the level of the ST segment [55] Such alterations will occur independently of any effect on ischemia In addition an agent such as insulin might reduce elevated extracellular potassium levels in the ischemic zone increase diastolic polarization of the cells and reduce the injury current The effects of such an agent on the ST segment need not necessarily imply improvement in ischemia or improved cellular prognosis

Caution is certainly required in interpreting ST segment displacement Although, in the experi mental animal, the sum of ST elevations at multiple precordial sites is closely related to the corresponding epicardial measurements [5] Smith and co workers were unable to demonstrate a simple quantitative relationship between ST segment elevation recorded from the epicardial surface of the canine heart and blood flow in the subjacent myocardium An increase in the size of the ischemic zone may actually reduce the magni tude of the injury current at epicardial sites [57] Nevertheless Angell and colleagues found a significant correlation between ST segment eleva tion at individual sites and intramyocardial O_2 tension 4 mm below the epicardial surface Measurements of ST segment displacement are invalid in records where intraventricular conduc tion block is apparent The limitations of ST segment mapping have been considered in detail by Fozzard and DasGupta Despite these limita tions the technique may have a place in the assessment of ischemia [“] The effects of the complex geometric relationship between bound aries separating ischemic and non ischemic tissues and the electrocardiogram have been analyzed by Holland and Brooks

Projection of QRS changes from early injury current Recently a series of electrocardiographic techniques has been developed which appears to be free from many of the problems associated with limiting the measurements to the ST segment The changes in the QRS complex result ing from infarction have been shown to be related to infarct size in the open-chest dog and to be predictable from the early displacement of the ST segment [6] The predictive value of ST segment elevation in the standard leads in relation to R wave diminution and the appearance of Q waves has been confirmed in the clinical situation The predictive value of ST elevation in relation to QRS change in precordial maps from patients with anterior infarction has also been con firmed [64] The time after onset of symptoms at which the leads showing ST elevation are assessed is of critical importance in estimating the likely disappearance of R waves [65]

An intervention introduced following the initial record may be shown to have altered the degree of change in the QRS complex to an extent which lies outside the limits of that expected The method is independent of any direct effect of therapy upon the ST segments and seems the most promising of the techniques currently avail able

Reduction of elevated filling pressure Eleva tion of the left ventricular filling pressure is rare when the heart rate is slow but clinically inap parent left ventricular defeat mild or moderate in degree is common among patients with normal or rapid rates Patients with anterior infarctio have on average higher filling pressures than those with posterior infarction [66] When the filling pressure is elevated a reduction may be effected by administration of a vasodilator agent There is evidence that substances such as sodium nitro prusside which dilate resistance vessels are un satisfactory for this purpose since they red ce myocardial perfusion whereas nitroglycerin in creases blood flow in the ischemic zone [9] The superiority of nitroglycerin may be explained by local effects on the coronary circulation but it may be relevant that in patients nitroglycerin a selective venodilator, caused a greater reduction in left ventricular filling pressure and a smaller reduction in arterial pressure than did sodium nitroprusside The data of Armstrong and asso ciates confirm that nitroglycerin selectively reduces the preload and that sodium nitroprus side has relatively greater effects on afterload and coronary perfusion pressure

Clinical evidence suggests that administration of nitroglycerin may reduce the extent of ische mia [9] However results from the animal labora tory indicate that if reduction in filling pressure is excessive hypotension with reflex tachycardia may result with possible intensification of ischemia Nitroglycerin may also precipitate bradycardia and hypotension in patients [11] The addition of a vasoconstrictor agent such as methoxamine or phenylephrine in doses sufficient to prevent tachycardia and hypotension will

result in greater improvement in the ischemic zone than will the administration of nitroglycerin alone[69, 74] Indiscriminate use of vasoconstrictor agents in conjunction with nitroglycerin cannot however be recommended since phenylephrine may partially reverse the salutary effect of nitro glycerin in patients with left ventricular fail ure[7]

Nitroglycerin has been administered by the sublingual route to patients with myocardial infarction without ill effect[75] However slow intravenous infusion is the only technique by which effective doses can be given safely over a period Titration of the individual dose is neces sary with careful monitoring of the heart rate and blood pressure[76] Administration of nitro glycerin is complicated by absorption of the drug by the tubing of the infusion equipment[7] Nevertheless nitroglycerin is the most effective venodilator agent available and if a relatively simple regime for its intravenous administration can be developed it may find a place in the management of a substantial proportion of patients with acute infarction

It has recently been shown that in the absence of infarction nitroglycerin administration in creases left ventricular compliance A possible mechanism for this effect is a reduction in pres sure applied to the interventricular septum from the right ventricular cavity An adequate cardiac output may therefore be maintained by improved diastolic function of non ischemic myocardium despite reduction in filling pres sure

Increasing osmotic pressure of extracellular fluid Osmotically active agents such as hyper tonic mannitol increase collateral blood flow in the presence of ischemia probably by reducing the swelling of ischemic cells[77] The reduction in coronary vascular resistance associated with mannitol administration following prolonged cor onary occlusion apparently includes reduction in the resistance of the vessels in the vulnerable subendocardial zone of the left ventricle[78] However mannitol exerts a direct positive inotropic effect[79] which may be undesirable Powell and co workers observed that mannitol had a salutary effect when coronary occlusion lasted 1 hour or less but Hirzel and Kirk[81] were unable to demonstrate any reduction in myocar dial damage when mannitol was administered during prolonged coronary occlusion Since reper fusion of formerly ischemic areas resulting from correction of autonomic disturbances may cause swelling of the tissues there may be a place for mannitol administration in conjunction with other interventions which are likely to improve blood flow to the ischemic zone

Pharmacological use of beta adrenergic block ing drugs While the value of beta blocking agents in the control of sympathetic overactivity is undoubted the possibility that these drugs may help to preserve jeopardized myoardium irrespec tive of the level of sympathetic activity has been investigated There is ample experimental and some clinical evidence that beta blocking agents may prevent hypoxic damage or limit the effects of ischemia[87, 8] In addition to the salutary effects on the myocardium ischemic microvascular inju ry may be reduced[8] It has been suggested that propranolol may prevent myocardial necrosis in some patients who would otherwise have devel oped infarction The administration of these agents to patients with bradycardia or hypoten sion is however contraindicated Furthermore bradycardia may follow their administration The routine use of beta adrenergic blocking drugs as a means of limiting infarct size cannot be recom mended unless the patient is to be continuously monitored so that bradycardia may be immedi ately detected

Verapamil and nifedipine Verapamil like the beta blocking drugs reduces cardiac work and in addition causes vasodilatation and may also have salutary effects[90] A further beneficial effect of verapamil and of the newer agent nifedipine is the release of coronary artery spasm which may be important in some patients

Agents acting at tissue level In the experimen tal situation the enzyme hyaluronidase has been shown to be effective in salvaging ischemic myocardium[91, 9] Preliminary clinical evidence supports the experimental results Hyaluroni dase may act by improving diffusion of substrates through ischemic tissue Another possible mecha nism is the preservation of collateral blood flow

Corticosteroid hormones in high dosage have been found to limit the effects of ischemia in the experimental animal[96] Steroids may act by preserving intracellular architecture and by improving metabolism and collateral blood flow[97] but evidence of benefit in clinical myocardial infarction is conflicting[8, 99, 101] A recent experi

mental investigation of the effects of methylprednisolone on final infarct size did not demonstrate any benefit, and the results suggested that the steroid increased ventricular irritability.[107] The data of Yoon and associates[1] [?] do not, however, support the latter proposition.

It has been suggested that the presence of any salutary effect of corticosteroids is limited to the first few hours after the onset of infarction.[104] The high affinity of cardiac tissue for steroids falls rapidly following the development of ischemia.

Potassium is rapidly depleted from ischemic cells, and aerobic metabolism of glucose is depressed. A regime consisting of glucose, insulin, and potassium (GIK) was devised by Sodi-Pallares and co-workers[*] with the object of reducing the amount of potassium lost. Opie[10] suggested that the regime may be beneficial through stimulation of glucose metabolism and reduction in the level of circulating free fatty acids (FFA).

Oliver[1] suggested that the possible salutary effects of therapeutic reduction of elevated FFA levels and of the stimulation of glucose uptake by the myocardium required further investigation. However, the relevance of the detrimental effects of experimental elevation of FFA on ischemic cardiac tissue has been questioned.[™] Nevertheless, evidence that increased catecholamine concentrations potentiate the adverse effects of FFA on the myocardium supports the hypothesis that FFA may have clinical relevance.[*]

The administration of GIK following coronary occlusion in the dog resulted in a reduction in plasma FFA levels, and a decrease in FFA uptake and an increase in glucose uptake by the myocardium. These effects were associated with evidence of metabolic improvement at the periphery of the ischemic zone.

The potential salutary effects of the constituents of the GIK regime are not restricted to the reduction of elevated FFA levels. Following coronary occlusion in a rat heart preparation glucose and insulin each reduced the release of cardiac enzymes resulting from the presence of fairly constant concentrations of FFA.

It is quite possible that elevated FFA levels in patients with myocardial infarction are indeed detrimental to jeopardized myocardium, and that reduction in these levels and of myocardial FFA uptake represent one important mechanism of the action of GIK therapy. Patients with relatively large infarcts have on average higher plasma FFA concentrations than those whose infarcts are small.[113] It has been proposed that high FFA levels play a part in promoting the vicious circle of extending infarction.[113]

As in the dog, GIK had favorable metabolic effects on infarcting baboon myocardium. Other experimental evidence indicates that the GIK regimen will have salutary effects on jeopardized myocardium.[115] Clinical evidence of such benefit is still, however, lacking.[116, 1]

Administration of oxygen. Hypoxemia is detrimental to ischemic myocardium.[1] Moreover, there is evidence that a moderate increase in inspired oxygen concentration above 20% may be salutary.[1] The data of Madias and co-workers[?] suggest that myocardial hypoxia may be reduced when oxygen in high concentration is administered to patients with myocardial infarction. These results support the already widespread clinical practice of administering oxygen even in the absence of signs of hypoxia.

Conclusion

It is clear that further work is required to define the place of the more recently introduced regimes in the routine management of patients with myocardial infarction. It is, however, important to recognize that shock may usually be prevented by such simple measures as the timely relief of pain and the immediate correction of disturbances of heart rate and rhythm and of blood pressure. Such disturbances commonly result from autonomic imbalance.

The crucial point in prevention of shock is the early initiation of therapy. Resources directed toward this end will undoubtedly result in greater reward than their direction toward complex circulatory support systems.

Fig. 1 is reproduced by kind permission of Pitman Medical, Tunbridge Wells, England.

REFERENCES

1. Scheidt, S., Alonso, D.R., Wilner, G., and Killip, T.: New concepts of cardiogenic shock. Preservation of ischemic myocardium. Bull. N. Y. Acad. Med. 50: 4 1974.
2. Page, D. L., Caulfield, J. B., Kastor, J. A., DeSanctis, R. W., and Sanders, C. A.: Myocardial changes associated with cardiogenic shock. N. Engl. J. Med. 285: 1... 1971.
3. Alonso, D. R., Scheidt, S., Post, M., and Killip, T.: Pathophysiology of cardiogenic shock, quantification of

myocardial necrosis clinical pathologic and electrocardiographic correlations Circulation 48 588 1973
4. McEnany M T Kay H R., Buckley M J Daggett W M Erdmann A J Mundth E D Rao R S De Toeuf J and Austen W G Clinical experience with intraaortic balloon pump support in 728 patients Circulation 58(Suppl I) 124 1978
5 Pantridge J F The effect of early therapy on the hospital mortality from acute myocardial infarction Q J Med 39 621 1970
6 Adgey A A J Allen J D Geddes J S James R G G., Webb S W., Zaidi, S A and Pantridge J F Acute phase of myocardial infarction Lancet 2 501 1971
7 Wackers, F J Lie K I Becker A E Durrer D and Wellens H J J Coronary artery disease in patients dying from cardiogenic shock or congestive heart failure in the setting of acute myocardial infarction Br Heart J 38 906 1976
8. Harnarayan C Bennett M A Pentecost B L and Brewer D B Quantitative study of infarcted myocardium in cardiogenic shock Br Heart J 32 728 1970
9 Maroko P R Kjekshus J K., Sobel B E Watanabe T Covell, J W Ross J Jr and Braunwald E Factors influencing infarct size following experimental coronary artery occlusions Circulation 43 67 1971
10 Gutovitz, A L Sobel, B E and Roberts R Progressive nature of myocardial injury in selected patients with cardiogenic shock Am J Cardiol 41 469 1978
11 Jennings R B and Reimer K A The fate of the ischemic myocardial cell, in Myocardial Infarction Corday E and Swan H J C eds Baltimore 1973 The Williams & Wilkins Co p 13
12 Jennings, R B Reimer K A and Lowe J E Pathologic evidence that infarct size can be limited in Abstracts VIII World Congress of Cardiology Tokyo Japan p 71 1978
13 Pantridge J F and Adgey A A J The pre hospital phase of acute myocardial infarction in Textbook of Coronary Care Meltzer L E and Dunning A J eds Amsterdam 1972 Excerpta Medica p 95
14 Graham T P Jr Covell J W Sonnenblick E H Ross J Jr and Braunwald E Control of myocardial oxygen consumption Relative influence of contractile state and tension development J Clin Invest 47 375 1968
15 Sonnenblick E H and Skelton C L Oxygen consumption of the heart Physiological principles and clinical implications Mod Concepts Cardiovasc Dis 40 9 1971
16 Mosher P Ross J Jr McFate P A and Shaw R F Control of coronary blood flow by an autoregulatory mechanism Circ Res 14 250 1964
17 Buckberg G D Fixler D F Archie J P and Hoffman J I E Experimental subendocardial ischemia in dogs with normal coronary arteries Circ Res 30 67 1972
18 Moir T W Coronary vascular adjustments to acute myocardial ischemia Arch Intern Med 129 799 1972
19 Brown B G Gundel W D Gott V L and Covell J W Coronary collateral flow following acute coronary occlusion A diastolic phenomenon Cardiovasc Res 8 621 1974
20 Robinson B F Collier J and Nachev Ch Changes in peripheral venous compliance after myocardial infarction Cardiovasc Res 6 67 1972
21 Clements I I Haemodynamic studies during the acute phase of myocardial infarction M D Thesis Queen s University of Belfast 19 7
22 Ogawa, T Vyden J K Rose H B Singh B N and Swan H J C Peripheral and central hemodynamics in acute myocardial infarction in Abstracts VIII World Congress of Cardiology Tokyo Japan p 143 1978
23 Pantridge J F Adgey A A J Geddes J S and Webb S W The Acute Coronary Attack Tunbridge Wells 1975 Pitman Medical New York 1975 Grune & Stratton Inc
24 Wyatt H L DaLuz P L Waters D D Swan H J C and Forrester J S Contrasting influences of alterations in ventricular preload and afterload upon systemic hemodynamics function and metabolism of ischemic myocardium Circulation 55 318 1977
25 Shell W E and Sobel B E Protection of jeopardized ischemic myocardium by reduction of ventricular afterload N Engl J Med. 291 481 1974
26 Franciosa J A Guiha N H Limas C J Paz S and Cohn J N Arterial pressure as a determinant of left ventricular filling pressure after acute myocardial infarction, Am J Cardiol. 34 506 1974
27 Henderson A H and Brutsaert D L An analysis of the mechanical capabilities of heart muscle during hypoxia Cardiovasc Res 7 63 1973
28 Oliva P B and Breckinridge J C Arteriographic evidence of coronary arterial spasm in acute myocardial infarction, Circulation 56 366 1977
29 Goldstein R E Stinson E B Scherer J L Seningen R. P Grehl T M and Epstein S E Intraoperative coronary collateral function in patients with coronary occlusive disease Nitroglycerin responsiveness and angiographic correlations Circulation 49 298 1974
30 Delgado C F Pitt B Taylor D R Weisfeldt M L and Kelly D T Role of sublingual nitroglycerin in patients with acute myocardial infarction Br Heart J 37 392 1975
31 Come P C and Pitt B Nitroglycerin induced severe hypoten ion and bradycardia in patients with acute myocardial infarction Circulation 54 624 1976
32 Chatterjee K and Swan H J C Hemodynamic profile of acute myocardial infarction in Myocardial Infarction Corday E and Swan H J C eds Baltimore 1973 The Williams & Wilkins Co p 51
33 Willerson J T Powell W J Jr Guiney T E Stark J J Sanders C A and Leaf A. Improvement in myocardial function and coronary blood flow in ischemic myocardium after mannitol J Clin Invest 51 2989 1972.
34 Diamond G and Forrester J S Effect of coronary artery disease and acute myocardial infarction on left ventricular compliance in man Circulation 45 11 1972
35 Theroux P Ross J Jr Franklin D., Covell J W., Bloor C M and Sasayama S Regional myocardial function and dimensions early and late after myocardial infarction in the unanesthetized dog Circ Res 40 158 1977
36 Vokonas P S Pirzada F A and Hood W B Jr Experimental myocardial infarction Dynamic changes in segmental mechanical behavior of infarcted and non infarcted myocardium Am J Cardiol 37 853 1976
37 Mathey D Bleifeld W., and Franken G Left ventricular relaxation and diastolic stiffness in experimental myocardial infarction Cardiovasc Res 8 583 1974
38 Mueller H S Ayres S M Religa A and Evans, R G Propranolol in the treatment of acute myocardial infarction Effect on myocardial oxygenation and hemodynamics Circulation 49 1078 1974
39 Williams D O Amsterdam E A and Mason D T

Hemodynamic effects of nitroglycerin in acute myocardial infarction Decrease in ventricular preload at the expense of cardiac output Circulation 51 421 1975
40 Kouwenhoven W B Jude J R and Knickerbocker G G Closed chest cardiac massage J A M A 173 1064 1960
41 Taylor G J Tucker W M Greene H L Rudikoff M T and Weisfeldt M L Importance of prolonged compression during cardiopulmonary resuscitation in man N Engl J Med. 296 1515 1977
42 Downey J Compression of the coronary arteries by the fibrillating canine heart Circ Res 39 53 1976
43 Berglund E Monroe R G and Schreiner G L Myocardial oxygen consumption and coronary blood flow during potassium induced cardiac arrest and during ventricular fibrillation Acta Physiol Scand 41 261 1957
44 Hottenrott C Maloney J V Jr and Buckberg G Studies of the effects of ventricular fibrillation on the adequacy of regional myocardial flow I Electrical vs spontaneous fibrillation J Thorac Cardiovasc Surg 68 615 1974
45 Dikshit K Vyden J K Forrester J S Chatterjee K Prakash R and Swan H J C Renal and extrarenal hemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction N Engl J Med 288 1087 1973
46 Watanabe T Covell J W Maroko P R Braunwald E and Ross J Jr Effects of increased arterial pressure and positive inotropic agents on the severity of myocardial ischemia in the acutely depressed heart Am J Cardiol 30 371 1972
47 Shell W E Kjekshus J K and Sobel B E Quantitative assessment of the extent of myocardial infarction in the conscious dog by means of analysis of serial changes in serum creatine phosphokinase activity J Clin Invest 50 2614 1971
48 Sobel B E Bresnahan G F Shell W E and Yoder R D Estimation of infarct size in man and its relation to prognosis Circulation 46 640 1972
49 Norris R M Whitlock R M L Barratt Boyes C and Small C W Clinical measurement of myocardial infarct size Modification of a method for the estimation of total creatine phosphokinase release after myocardial infarction Circulation 51 614 1975
50 Sobel B E Markham J and Roberts R Factors influencing enzymatic estimates of infarct size Am J Cardiol 39 130 1977
51 Roberts R Henry P D and Sobel B E An improved basis for enzymatic estimation of infarct size Circulation 52 743 1975
52 Roe C R and Starmer C F A sensitivity analysis of enzymatic estimation of infarct size Circulation 52 1 1975
53 Maroko P R Libby P Covell J W Sobel B E Ross J Jr and Braunwald E Precordial S T segment elevation mapping An atraumatic method for assessing alterations in the extent of myocardial ischemic injury The effects of pharmacologic and hemodynamic interventions Am J Cardiol 29 223 1972
54 Muller J E Maroko P R and Braunwald E Evaluation of precordial electrocardiographic mapping as a means of assessing changes in myocardial ischemic injury Circulation 52 16 1975
55 Toyoshima H Prinzmetal M Horiba M Kobayashi T, Mizuno Y, Nakayama R and Yamada K The nature of normal and abnormal electrocardiograms VIII Relation of ST segment and T wave changes to intracellular potentials Arch Intern Med. 115 4 1965
56 Smith H J Singh B N Norris R M John M B and Hurley P J Changes in myocardial blood flow and S T segment elevation following coronary artery occlusion in dogs Circ Res 36 697 1975
57 Cohen M V and Kirk E S Reduction of epicardial ST segment elevation following increased myocardial ischemia Experimental and theoretical demonstration (Abstr) Clin Res 22 269A 1974
58 Angell C S Lakatta E G Weisfeldt M L, and Shock N W Relationship of intramyocardial oxygen tension and epicardial ST segment changes following acute coronary artery ligation effects of coronary perfusion pressure Cardiovasc Res 9 12 1975
59 Fozzard H A and DasGupta D S ST segment potentials and mapping Theory and experiments. Circulation 54 533 1976
60 Braunwald E and Maroko P R ST segment mapping Realistic and unrealistic expectations Circulation 54 529 1976
61 Holland R P and Brooks H Precordial and epicardial surface potentials during myocardial ischemia in the pig A theoretical and experimental analysis of the TQ and ST segments Circ Res 37 471 1975
62 Hillis L D Askenazi J Braunwald E Radvany P Muller J E Fishbein M C and Maroko P R Use of changes in the epicardial QRS complex to assess interventions which modify the extent of myocardial necrosis following coronary artery occlusion Circulation 54 591 1976
63 Askenazi J Maroko P R Lesch M and Braunwald, E Usefulness of ST segment elevations as predictors of electrocardiographic signs of necrosis in patients with acute myocardial infarction Br Heart J 39 64 1977
64 Selwyn A P Ogunro E and Shillingford J P Loss of electrically active myocardium during anterior infarction in man Br Heart J 39 1186 1977
65 Selwyn A P Fox K M Welman E Jonathan A and Shillingford J P Electrocardiographic precordial mapping in anterior myocardial infarction The critical period for interventions as exemplified by methylprednisolone Circulation 58 892 1978
66 Russell R O Jr Hunt D and Rackley C E Left ventricular hemodynamics in anterior and inferior myocardial infarction Am J Cardiol 32 8 1973
67 Chiariello M Gold H K Leinbach R C Davis M A and Maroko P R Comparison between the effects of nitroprusside and nitroglycerin on ischemic injury during acute myocardial infarction Circulation 54 766 1976
68 Armstrong P W Walker D C Burton J R and Parker J O Vasodilator therapy in acute myocardial infarction A comparison of sodium nitroprusside and nitroglycerin Circulation 52 1118 1975
69 Borer J S Redwood D P Levitt B Vallin H Reicher Reiss H Bianchi C Epstein S E and Sowton E Nitroglycerin and nitroglycerin phenylephrine induced reduction in ischaemia during acute myocardial infarction in man (Abstr) Br Heart J 37 783 1975
70 Flaherty J T Reid P R Kelly D T Taylor D R, Weisfeldt M L and Pitt B Intravenous nitroglycerin in acute myocardial infarction Circulation 51 132 1975
71 Flaherty J T Come P C Baird M G Rouleau J

Taylor D R Weisfeldt M L Greene H L Becker L C, and Pitt, B Effects of intravenous nitroglycerin on left ventricular function and ST segment changes in acute myocardial infarction Br Heart J 38 61? 1976.

7? Epstein S E Borer J S Kent K M Redwood D R Goldstein R E and Levitt B Protection of ischemic myocardium by nitroglycerin Experimental and clinical results, Circulation 53 (Suppl I) 191 1976

73 Derrida J P, Sal R, and Chiche P Nitroglycerin infusion in acute myocardial infarction N Engl J Med 297 336 1977

74 Epstein S E Kent K M Goldstein R E Borer J S, and Redwood D R Reduction of ischemic injury by nitroglycerin during acute myocardial infarction N Engl J Med 292 29 1975

75 Awan N A, Amsterdam E A Vera Z, DeMaria A N Miller R R, and Mason D T Reduction of ischemic injury by sublingual nitroglycerin in patients with acute myocardial infarction Circulation 54 761 1976

76. Cossum, P A, Galbraith, A J, Roberts M S and Boyd G W Loss of nitroglycerin from intravenous infusion sets Lancet 2 349 19 8

77 Ludbrook P A Byrne J D Kurnik P B, and McKnight R C Influence of reduction of preload and afterload by nitroglycerin on left ventricular diastolic pressure volume relations and relaxation in man Circulation 56 937 1977

78 Willerson J T Watson J T, Hutton I Templeton G H, and Fixler D E Reduced myocardial reflow and increased coronary vascular resistance following prolonged myocardial ischemia in the dog Circ Res 36 771 1975

79 Willerson J T Weisfeldt M L Sanders C A and Powell, W J Jr Influence of hyperosmolar agents on hypoxic cat papillary muscle function Cardiovasc Res 8 8 1974

80 Powell W J Jr DiBona D R Flores J and Leaf A The protective effect of hyperosmotic mannitol in myocardial ischemia and necrosis Circulation 54 603 19 6

81 Hirzel H O and Kirk E S The effect of mannitol following permanent coronary occlusion Circulation 56 1006 1977

82. Pelides L J Reid D S Thomas M, and Shillingford J P Inhibition by beta blockade of the ST segment elevation after acute myocardial infarction in man Cardiovasc Res 6 295 19 2.

83 Reimer K A Rasmussen M M and Jennings R B Reduction by propranolol of myocardial necrosis following temporary coronary artery occlusion in dogs Circ Res 33 353 1973

84 Libby P, Maroko P R Covell J W Malloch, C I Ross J Jr and Braunwald E Effect of practolol on the extent of myocardial ischaemic injury after experimental coronary occlusion and its effects on ventricular function in the normal and ischaemic heart Cardiovasc Res 7 167 1973

85 Nayler W G Grau A and Yepez G Beta adrenoceptor antagonists and the release of creatine phosphokinase from hypoxic heart muscle Cardiovasc Res. 11 344 1977

86 Hillis D Khuri, S Kloner R Tow D Barsamian E Maroko P and Braunwald E Direct evidence for the beneficial effect of propranolol on myocardial ischemia following coronary artery occlusion (Abstr) Am J Cardiol. 41 359 1978

87 Peter T, Norris, R M Clarke E D Heng M K, Singh B N, Williams, B, Howell D R and Ambler P K Reduction of enzyme level by propranolol after acute myocardial infarction Circulation 57 1091 1978

88 Rasmussen M M, Reimer K A Kloner R A, and Jennings R B Infarct size reduction by propranolol before and after coronary ligation in dogs Circulation 56 794 1977

89 Norris R M, Clarke E D Sammel, N L, Smith W M, and Williams, B Protective effect of propranolol in threatened myocardial infarction Lancet 2 907 1978

90 Smith H J Singh, B N Nisbet H D and Norris, R M Effects of verapamil on infarct size following experimental coronary occlusion Cardiovasc Res. 9 569 1975

91 Braunwald E Maroko P R, and Libby P Reduction of infarct size following coronary occlusion Circ Res 34 and 35 (Suppl III) 19? 19 4

92 Ribeiro L G T, Hillis L D, Louie E K, Davis M A, Maroko P R and Braunwald E A method for demonstrating the efficacy of interventions designed to limit infarct size following coronary occlusion Beneficial effect of hyaluronidase Cardiovasc Res 12 334 1978.

93. Kloner R A Braunwald E, and Maroko P R Long term preservation of ischaemic myocardium in the dog by hyaluronidase Circulation 58 220 1978

94 Maroko P R Davidson D M, Libby P, Hagan A D, and Braunwald E. Effects of hyaluronidase administration on myocardial ischemic injury in acute infarction A preliminary study in 24 patient Ann Intern Med. 82 516 19 5

95 Askenazi, J Hillis L D Diaz P E, Davis M A Braunwald E, and Maroko P R The effects of hyaluronidase on coronary blood flow following coronary artery occlusion in the dog Circ Res 40 566 1977

96. Libby P, Maroko P R Bloor C M Sobel B E and Braunwald E Reduction of experimental myocardial infarct size by corticosteroid administration J Clin Invest 52 599 1973

97 Shatney C H MacCarter D J, and Lillehei, R. C Effects of allopurinol propranolol and methylprednisolone on infarct size in experimental myocardial infarction Am J Cardiol 37 572 19 6

98. Spath J A Lane D L and Lefer A M Protective action of methylprednisolone on the myocardium during experimental myocardial ischemia in the cat Circ Res 35 44 1974

99 Masters T N Harbold M B Jr Hall D G Jackson R. D Mullen D C Daugherty H K and Robicsek F Beneficial metabolic effects on methylprednisolone sodium succinate in acute myocardial ischemia Am J Cardiol 37 557 19 6

100 Morrison J Reduto L Pizzarello R Geller K Maley T and Culotta S Modification of myocardial injury in man by corticosteroid administration Circulation 53(Suppl. I) 200 19 6

101 Roberts R De Mello V and Sobel, B E Deleterious effects of methylprednisolone in patients with myocardial infarction Circulation 53(Suppl I) 204 1976

102 Vogel W M, Zannoni V G Abrams G D and Lucchesi, B R Inability of methylprednisolone sodium succinate to decrease infarct size or preserve enzyme activity measured 24 hours after coronary occlusion in the dog Circulation 55 588 1977

103 Yoon M S Goel B G and Han J Effects of

methylprednisolone on ventricular arrhythmias during acute myocardial ischaemia, Cardiovasc Res 13 58 1979
104. Lefer A. M Editorial Glucocorticoids in myocardial infarction, Circ Shock 3 263, 1976
105 Okuda, M., Young K. R., Jr., and Lefer A M Localization of glucocorticoid uptake in normal and ischemic myocardial tissue of isolated perfused cat hearts Circ Res. 39 640 1976
106 Sodi Pallares, D., Bisteni, A. Medrano G A., Testelli, M. R., and De Micheli, A. The polarizing treatment of acute myocardial infarction Possibility of its use in other cardiovascular conditions. Dis Chest 4 424 1963
107 Opie L. H. The glucose hypothesis Relation to acute myocardial ischaemia J Molec Cell. Cardiol 1 107 1970
108 Oliver M. F Metabolic response during impending myocardial infarction II Clinical Implications Circulation 45 491 1972.
109 Opie L. H Metabolic response during impending myocardial infarction I. Relevance of studies of glucose and fatty acid metabolism in animals Circulation 45 483 1972.
110 Opie L. H Metabolism of free fatty acids glucose and catecholamines in acute myocardial infarction Relation to myocardial ischemia and infarct size Am J Cardiol. 36 938 1975
111. Opie L. H., and Owen, P Effect of glucose insulin potassium infusions on arteriovenous differences of glucose and of free fatty acids and on tissue metabolic changes in dogs with developing myocardial infarction Am. J Cardiol. 38 310 1976
112. De Leiris, J., and Opie L. H Effect of substrates and of coronary artery ligation on mechanical performance and on release of lactate dehydrogenase and creatine phosphokinase in isolated working rat hearts, Cardiovasc Res 12 585 1978
113 Opie L. H., Tansey M., and Kennelly B M. Proposed metabolic vicious circle in patients with large myocardial infarcts and high plasma free fatty acid concentrations Lancet 2 890 1977
114 Opie L. H., Bruyneel, K. and Owen, P Effects of glucose insulin and potassium infusion on tissue metabolic changes within first hour of myocardial infarction in the baboon Circulation 52 49 1975
115 Maroko P R., Libby P., Sobel, B E Bloor C M, Sybers H D., Shell, W E., Covell, J W and Braunwald E Effect of glucose insulin-potassium infusion on myocardial infarction following experimental coronary artery occlusion Circulation 45 1160 1972
116 Heng, M K., Norris R. M., Singh, B N and Barratt-Boyes C Effects of glucose and glucose insulin-potassium on haemodynamics and enzyme release after acute myocardial infarction Br Heart J 39 748 1977
117 Rogers W J., Segall, P H., Mantle J A., McDaniel H G., Russell, R O Jr., and Rackley C E Glucose insulin potassium in myocardial infarction A randomized study (Abstr) Circulation 55 and 56(Suppl. III) 67 1977
118. Radvany P Maroko P R., and Braunwald E. Effects of hypoxemia on the extent of myocardial necrosis after experimental coronary occlusion Am. J Cardiol 35 795 1975
119 Maroko P R., Radvany P., Braunwald, E and Hale S L. Reduction of infarct size by oxygen inhalation following acute coronary occlusion, Circulation 52 360 1975
120 Madias J E Madias N E and Hood, W B J Precordial ST-segment mapping 2. Effects of oxygen inhalation on ischemic injury in patients with acute myocardial infarction Circulation 53 411 1976

Clinical pharmacology of the new beta-adrenergic blocking drugs Part 10 Beta adrenoceptor blockade and coronary artery surgery

Yasu Oka M D
William Frishman M D *
Ronald M Becker M D
Alan Kadish M D
Joel Strom M D
Masayuki Matsumoto M D
Louis Orkin M D
Robert Frater M B Ch B M S
Bronx N Y

Beta adrenoceptor blocking drugs are important therapeutic agents in the medical management of patients with angina pectoris hypertension cardiac arrhythmias thyrotoxicosis pheochromocytoma and obstructive cardiomyopathies[1] An increasing number of patients can be expected to present for surgical anesthesia while taking beta adrenoceptor blocking drugs

During the past several years recommendations regarding treatment of patients receiving propranolol and who were scheduled for coronary artery bypass operations have varied widely These recommendations have ranged from the complete withdrawal of therapy two weeks prior to surgery to the continuation of therapy at the same or lesser dosage just prior to the operation Reports associating the abrupt withdrawal of long term propranolol therapy with an increase in angina new arrhythmias myocardial infarction or sudden death have raised the issue of whether the risk of such withdrawal before coronary bypass operation is greater than the risk of purported myocardial depression attributed to interaction between residual β adrenoceptor blockade and general anesthesia[2]

Recent retrospective and prospective reviews of consecutive coronary artery bypass operations in which propranolol therapy was not withdrawn for medical indications failed to identify any deleterious interaction between anesthesia and preoperative propranolol administration[3] [4] Moreover anesthetic agents commonly used for bypass operations have been shown in animals not to potentiate the effects of propranolol

In a previous study in patients who underwent coronary artery bypass surgery our group described a higher incidence of postoperative arrhythmias and hypertension in individuals withdrawn from propranolol preoperatively when compared to a population who either never received the drug or had the drug maintained postoperatively[5] We therefore undertook this prospective study to elucidate the mechanism for these phenomena Our protocol was designed to answer the following questions (1) Are there hazards associated with either preoperative maintenance or withdrawal of propranolol therapy? (2) Are there hazards related to persisting β blockade during intubation general anesthesia and coronary artery bypass surgery? (3) Does persisting β blockade lead to poor cardiac per

From th D p tm ts f Anesth siology Med nd Surg ry Th Albert Fin tein Coll g of M d n Bro N Y

R ed f publ ation N 16 1979

R pri t equ t Y su Ok M D D pt f A esthesi logy Albert Ein t Coll ge of Med e 1300 M rris Park A e Bro N Y 10461

D Frishma is a Te hing S holar f th Am rican Heart Associa t

000? 8703/80/02025o + 1o$01 50/0 © 1980 The C V Mosby Co

methylprednisolone on ventricular arrhythmias during acute myocardial ischaemia, Cardiovasc. Res. 13 58 1979
104 Lefer A. M Editorial Glucocorticoids in myocardial infarction, Circ. Shock 3 263 1976
105 Okuda, M., Young K R., Jr and Lefer A. M Localization of glucocorticoid uptake in normal and ischemic myocardial tissue of isolated perfused cat hearts Circ Res 39 640 1976
106 Sodi Pallares, D., Bisteni, A. Medrano G A., Testelli, M R., and De Micheli, A The polarizing treatment of acute myocardial infarction Possibility of its use in other cardiovascular conditions, Dis. Chest 4 424 1963.
107 Opie L. H The glucose hypothesis Relation to acute myocardial ischaemia, J Molec Cell. Cardiol. 1 107 1970
108 Oliver M F Metabolic response during impending myocardial infarction II Clinical Implications Circulation 45 491 1972
109 Opie L. H Metabolic response during impending myocardial infarction I Relevance of studies of glucose and fatty acid metabolism in animals Circulation 45 483, 1972.
110 Opie L. H Metabolism of free fatty acids glucose and catecholamines in acute myocardial infarction Relation to myocardial ischemia and infarct size Am J Cardiol. 36 938 1975
111 Opie L. H., and Owen, P Effect of glucose insulin potassium infusions on arteriovenous differences of glucose and of free fatty acids and on tissue metabolic changes in dogs with developing myocardial infarction Am. J Cardiol. 38 310 1976
112 De Leiris, J and Opie L. H Effect of substrates and of coronary artery ligation on mechanical performance and on release of lactate dehydrogenase and creatine phosphokinase in isolated workin rat hearts, Cardiovasc. Res. 12 585 1978
113 Opie L. H Tansey M and Kennelly B M. Proposed metabolic vicious circle in patients with larg myocardial infarcts and high plasma free fatty acid concentrations Lancet 2 890 1977
114 Opie L. H., Bruyneel, K. and Owen P Effects of glucose insulin and potassium infusion on tissue metabolic changes within first hour of myocardial infarction in the baboon Circulation 52 49 1975.
115 Maroko P R., Libby P., Sobel, B E., Bloor C M., Sybers H D., Shell, W E., Covell, J W and Braunwald, E Effect of glucose-insulin potassium infusion on myocardial infarction following experimental coronary artery occlusion Circulation 45 1160 1972
116 Heng M K. Norris R M., Singh, B N and Barratt Boyes C Effects of glucose and glucose-insulin potassium on haemodynamics and enzyme release after acute myocardial infarction Br Heart J 39 748 1977
117 Rogers W J Segall, P H Mantle J A., McDaniel H. G., Russell, R. O., Jr., and Rackley C E Glucose-insulin potassium in myocardial infarction A randomized study (Abstr) Circulation 55 and 56(Suppl. III) 66 1977
118. Radvany P Maroko P R., and Braunwald E Effects of hypoxemia on the extent of myocardial necrosis after experimental coronary occlusion Am J Cardio 35 795 1975
119 Maroko P R., Radvany P., Braunwald, E., and Hale S L. Reduction of infarct size by oxygen inhalation following acute coronary occlusion, Circulation 52 3?? 1975
120 Madias J E., Madias N E and Hood, W B J Precordial ST segment mapping 2. Effects of oxy inhalation on ischemic injury in patients with ac myocardial infarction, Circulation 53 411 1976

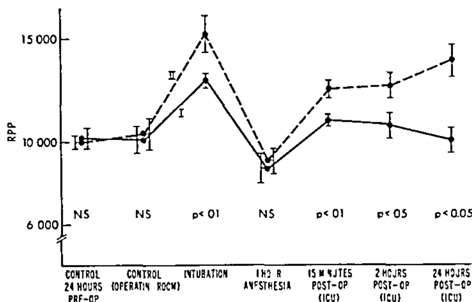


Fig 1 Mean rate-pressure product *(RPP)* of group I patients (no propranolol) and group II patients (propranolol discontinued 48 hours preop) before during and after coronary artery surgery Group I is shown with a *solid line* group II with a *broken line* Group II patients demonstrate a significant increment in RPP during intubation and the postoperative intervals when compared to group I patient The values refer to the differences between groups at the different study intervals *NS* = not significant

Table II Characteristics of patient groups

Group	Patient number	Age (years)	Sex M F	LVEDP mm Hg	No of Grafts	Propranolol dose (mg/day)	Previous myocardial infarct (% of group)	Previous hypertension (% of group)
I	17	59 ± 1	11–6	14 ± 1	2.3 ± 0.2	–	23% (4/17)	35% (6/17)
II	17	53 ± 2	11 6	14 ± 1	2.3 ± 0.2	154 ± 18	23% (4/17)	41% (7/17)
III	18	55 ± 2	12 6	15 ± 2	2.4 ± 0.2	151 ± 15	28% (5/18)	28% (5/18)
IV	19	56 ± 2	11 8	15 ± 1	2.5 ± 0.2	133 ± 0	26% (5/19)	32% (6/19)

Abbreviations LVEDP = left ventricular end-diastolic pressure

plications as well as the need for cardioactive agents until hospital discharge were recorded

Blood specimens for plasma propranolol levels were obtained at the time of induction after cardiopulmonary bypass and immediately upon arrival in the intensive care unit Measurements were made using the modified fluorometric method of Coltart and Shand

Blood specimens for plasma renin activity were obtained several times in the operating room prior to induction (control) immediately after intubation and following surgery (15 minutes and 2 hours) The renin measurements were made by the radioimmunoassay technique of Chervu and associates

The significance of differences in incidence between groups was determined by chi square analysis and differences in means of quantitative data were derived using Student s t test for non paired data The standard error of the mean was used as the index of dispersion

Results

The four patient groups were remarkably homogenous for patient characteristics such as sex history of hypertension and previous myocar

Table III Effects of different propranolol regimens on heart rate systolic blood pressure and rate pressure product in patients undergoing coronary artery bypass surgery

Observation period	*Group I (no propranolol)*	*Group II (propranolol stopped 48 hrs preop)*	*Group III (propranolol stopped 10 hrs postop)*	*Group IV (propranolol stopped 2 hrs preop continued postop)*		
					Group 1 vs Group 2	*Group I vs Group 3*
Control (24 hrs preop)						
hr	79 ± 3	76 ± 3	72 ± 2	70 ± 2	NS	NS
bp	131 ± 4	132 ± 3	122 ± 6	125 ± 3	NS	NS
rpp	10 200 ± 485	10 000 ± 364	8 500 ± 436	8 600 ± 252	NS	<0 01
Control (immed preop)						
hr	78 ± 4	79 ± 3	66 ± 5	67 ± 3	NS	<0 01
bp	130 ± 6	132 ± 4	118 ± 5	114 ± 3	NS	NS
rpp	10 100 ± 655	10 400 ± 752	7 700 ± 485	7 700 ± 275	NS	<0 05
Intubation						
hr	71 ± 2	80 ± 2	84 ± 4	71 ± 3	<0 01	<0 01
bp	180 ± 7	190 ± 6	173 ± 7	154 ± 5	NS	NS
rpp	13 000 ± 364	15 300 ± 846	14 500 ± 1 116	11 200 ± 458	<0 01	NS
1 hr anesthesia						
hr	73 ± 4	76 ± 4	75 ± 3	66 ± 1	NS	NS
bp	115 ± 5	120 ± 4	125 ± 7	108 ± 4	NS	NS
rpp	8 742 ± 723	9 100 ± 631	9 235 ± 543	7 817 ± 596	NS	NS
15 min postop (ICU)						
hr	84 ± 3	97 ± 3	88 ± 2	80 ± 3	<0 01	NS
bp	132 ± 3	131 ± 4	132 ± 5	135 ± 4	NS	NS
rpp	11 100 ± 242	12 600 ± 436	11 700 ± 631	10 400 ± 435	<0 01	NS
2 hrs postop (ICU)						
hr	84 ± 7	96 ± 4	92 ± 5	79 ± 2	NS	NS
bp	130 ± 4	136 ± 3	144 ± 7	136 ± 3	NS	NS
rpp	10 800 ± 655	12 800 ± 582	13 300 ± 800	10 400 ± 435	p<0 05	p<0 05
24 hrs postop (ICU)						
hr	84 ± 2	105 ± 5	96 ± 3	77 ± 2	<0 01	<0 01
bp	116 ± 3	137 ± 7	140 ± 7	120 ± 4	<0 01	<0 01
rpp	10 100 ± 582	14 000 ± 776	13 400 ± 946	9 300 ± 389	<0 05	<0 05

dial infarction duration of anesthesia duration of cardiopulmonary bypass and number of coronary vessels bypassed There were no differences between the groups in the ease of discontinuing cardiopulmonary bypass

There were five perioperative infarctions (new Q waves) seen with one death The incidence of infarction among the different groups was group I 6% (1 of 17) group II 18% (3 of 17) group III 6% (1 of 18) group IV 0% (none of 19) The one death occurred in a group II patient 28 hours after surgery from low cardiac output as a consequence of infarction

The hemodynamic results are shown in Table III and in Figs 1 to 6 During the control period (24 hours prior to surgery) patients in groups III and IV (both groups still receiving propranolol) had significantly lower mean rate pressure products (RPP) than group I and II patients During the control period immediately prior to surgery patients in groups III and IV continued to have significantly lower RPP than group I and II patients

With intubation there was a dramatic increase in RPP in all four groups predominantly due to a marked systolic blood pressure elevation (in some patients up to 280 mm Hg) However the RPP increment in group IV patients was significantly blunted compared to groups I to III At the same time the RPP value for group IV was significantly lower than that of the other three groups Group I patients (no propranolol) also had a lower RPP increment than group II and III patients

After one hour of halothane anesthesia the blood pressure and RPP returned to near control levels (24 hours preop) for all groups however group IV continued to have a significantly lower RPP than the other three groups

Statistical Significance

Group 1 vs Group 4	Group 2 vs Group 3	Group 2 vs Group 4	Group 3 vs Group 4
<0.01	NS	NS	NS
NS	NS	NS	NS
<0.01	<0.05	<0.01	NS
<0.01	<0.05	<0.01	NS
<0.01	<0.05	<0.01	NS
<0.05	<0.01	<0.01	NS
NS	NS	<0.05	<0.05
<0.05	NS	<0.01	<0.01
<0.01	NS	<0.01	<0.01
<0.05	NS	<0.05	<0.05
NS	NS	<0.05	<0.05
NS	NS	NS	<0.05
NS	<0.05	<0.01	<0.05
NS	NS	NS	NS
NS	NS	<0.01	NS
NS	NS	<0.01	<0.05
NS	NS	NS	NS
NS	NS	<0.01	<0.01
<0.05	NS	<0.01	<0.01
NS	NS	<0.05	<0.05
NS	NS	<0.01	<0.01

Fifteen minutes following surgery in the ICU the RPP was found to rise in all four groups (though not as markedly as during intubation). Group II patients had the highest increment in both pulse rate and RPP compared with the three other groups. Group I and group IV patients appeared to react similarly.

Two hours later patients in group *III* were found to have a greater increment in heart rate and RPP compared to 15 minutes postop. At this point groups II and III were similar with a higher heart rate and RPP than groups I and IV.

Twenty four hours post surgery the heart rate blood pressure and RPP continued to climb in both groups II and III (with the RPP almost to the level found during intubation). The blood pressure heart rate and RPP in groups I and IV remained significantly lower than in groups II and III.

There was a significant difference in the incidence of supraventricular arrhythmias among the four study groups (Table IV, Fig 7) during the initial 24 hour postoperative period. In group I seven patients remained in normal sinus rhythm and 10 developed supraventricular arrhythmias (six sinus tachycardia >110, four paroxysmal supraventricular tachycardia or atrial flutter). Group II patients had the highest incidence of supraventricular arrhythmias among the four study groups. One patient remained in normal sinus rhythm and 16 developed supraventricular arrhythmias (eight sinus tachycardia >110 and eight paroxysmal supraventricular tachycardia or atrial flutter fibrillation). Group III patients also had a high incidence of supraventricular arrhythmias. Three patients remained in normal sinus rhythm and 15 developed arrhythmias (seven sinus tachycardia >110, eight paroxysmal supraventricular tachycardia or atrial flutter fibrillation). The incidence of arrhythmia was significantly higher in group II ($p < 0.01$) and group III ($p < 0.05$) when compared to groups I and IV. Group IV had a significantly lower incidence of supraventricular arrhythmia than the other three treatment groups ($p < 0.01$). Fourteen patients were in normal sinus rhythm *and five developed arrhythmias (three sinus* tachycardia >110 and two paroxysmal atrial tachycardia or atrial flutter fibrillation). All paroxysmal arrhythmia episodes in each group responded to intravenous propranolol (or supplementary propranolol in group IV patients). Ventricular arrhythmias were rarely seen in the initial 24 hour postoperative period.

Plasma renin activity (PRA) was lower in group IV patients compared to all other groups throughout the control intubation and postoperative periods. There were no significant differences in PRA between groups II to IV during the intubation and postoperative intervals. Comparing group I and IV the results were: control (operating room) group I 1.13 ± 0.04 ng/ml/hr, group IV 0.96 ± 0.11 ng/ml/hr; after intubation group I 1.36 ± 0.26 ng/ml/hr, group IV 0.98 ± 0.12 ng/ml/hr; 15 minutes postoperation group I 1.86 ± 0.10 ng/ml/hr, group IV 0.95 ± 0.15 ng/ml/hr ($p < 0.01$); 2 hours postoperation group I 1.66 ± 0.53 ng/ml/hr, group IV 1.08 ± 0.19 ng/ml/hr.

Propranolol plasma levels at the time of intubation were negligible for group II patients and

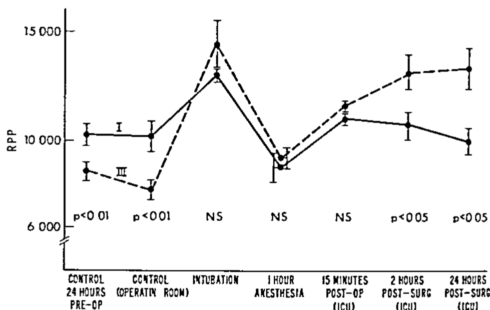


Fig 2 Mean rate pressure product *(RPP)* of group I patients (no propranolol) and group III patients (propranolol discontinued 10 hours preop) before during and after coronary artery surgery Group I is shown with a *solid line* group III with a *broken line* Group III patients had significantly lower RPP (probably due to persistence of beta adrenoceptor blocker effect) than group I during the preoperative intervals. However with intubation there is no difference between groups. Two hours and 24 hours postoperatively the RPP is significantly higher in group III patients compared to group I patients.

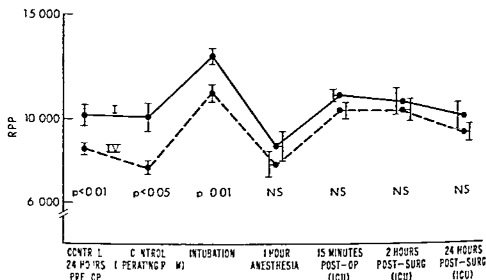


Fig 3 Mean rate pressure product *(RPP)* of group I patients (no propranolol) and group IV patients (propranolol maintained until hours preop restarted immediately postop) before during and after coronary artery surgery Group I is shown with a *solid line* group IV with a *broken line* Group IV patients had significantly lower RPP than group I patients during the preoperative intervals. The increment in RPP with intubation was significantly blunted in group IV patients The operative and postoperative differences in RPP between groups were not significant

9 32 ± 0 82 ng ml in group III patients (minimal therapeutic level >40 ng ml) One hour after cardiopulmonary bypass the drug level in group III declined progressively to 3 [illegible] ± 0 [illegible]0 ng /ml so that in the immediate postoperative period it was negligible 2 26 ± 0 22 ng ml Renal clearance of propranolol increased considerably during cardiopulmonary bypass Group IV patients had a plasma propranolol level of 39 1 ± 1 17 ng /ml at the time of induction which decreased considerably post cardiopulmonary bypass to 5 2 ± 0 80 ng /ml

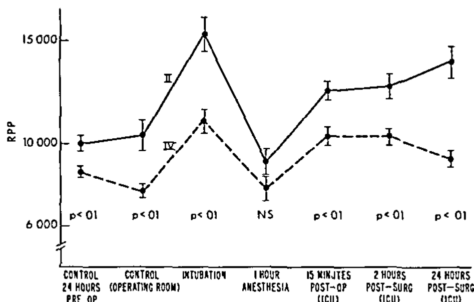


Fig 4 Mean rate pressure product *(RPP)* of group II patients (propranolol discontinued 48 hours preop) and group IV patients (propranolol maintained until 2 hours preop restarted immediately) before during and after coronary artery surgery Group II is shown with a *solid line* group IV with a *broken line* Group IV patients had significantly lower RPP at each study interval compared to group II patients

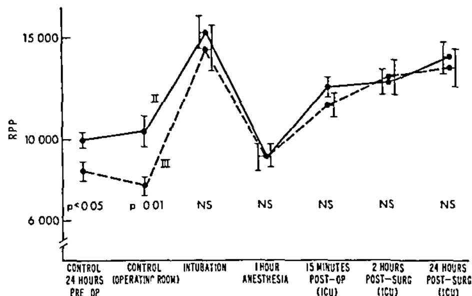


Fig 5 Mean rate pressure product *(RPP)* of group II patients (propranolol discontinued 48 hours preop) and group III patients (propranolol discontinued 10 hours preop) before during and after *coronary artery surgery* Group II is shown with a *solid line* group III with a *broken line* Group III patients had significantly lower RPP during the preoperative periods however there were no differences between the groups during the other study intervals A marked increment in RPP during intubation and the postoperative periods was seen

Discussion

Since the discovery by Powell and Slater[23] that the dichloro *analogue of isoproterenol could completely* inhibit the effects of catecholamines on the heart a number of beta adrenoceptor blocking agents have been synthesized and subjected to clinical evaluation Although the therapeutic value of these drugs is well established for angina pectoris hypertension arrhythmias hypertrophic obstructive cardiomyopathy thyrotoxic tachycardia and pheochromocytoma the attitudes of anesthesiologists and surgeons to their

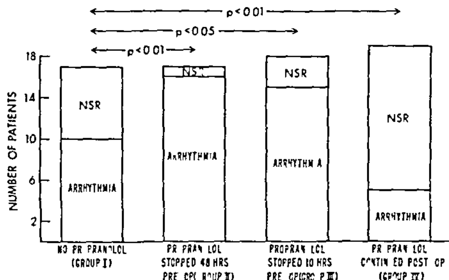


Fig 7 The incidence of supraventricular arrhythmias post-coronary artery bypass in the different propranolol treatment groups There was a significant increase in the frequency of arrhythmias in group II patients (propranolol discontinued 48 hours preop and group III patients (propranolol discontinued 10 hours preop) compared to group I (no propranolol) Group IV patients (propranolol maintained postop) had a significantly lower incidence of arrhythmias compared to group I patients (no propranolol)

nary artery disease who received propranolol (100 to 320 mg) to within 24 hours of surgery four of these patients died and one had a stormy postoperative course The authors concluded that propranolol was a major factor in these deaths and therefore recommended that it be discontinued for two weeks before operations However close scrutiny reveals that these five cases were complicated by other factors and it is difficult to implicate propranolol alone as the cause for the complications seen

In 1973 Faulkner and colleagues demonstrated that any negative inotropic effects of propranolol had disappeared by 48 hours and suggested that the recommendation of Viljoen and colleagues for a two week preoperative withdrawal period was unfounded

In 1974 Caralps and associates reviewed 100 cases of coronary artery bypass surgery including 25 patients who were receiving 40 to 200 mg of propranolol 24 hours or less before the operation They revealed that the operative course of patients receiving propranolol many of whom had unstable angina was no different from that of untreated patients In a larger review of 303 patients who underwent coronary artery surgery the same investigators found that propranolol treated subjects (48 hours or less prior to surgery) not only tolerated the operative procedure well but demonstrated a low mortality rate (3.8% for patients receiving propranolol vs 6.6% for those never receiving the drug)

In 1975 Kaplan and associates reviewed the records of 169 consecutive patients undergoing coronary artery bypass surgery of whom 143 had been taking propranolol with regard to preoperative administration of propranolol and intraoperative or postoperative complications Patients taking propranolol until 24 hours before surgery showed no increased incidence of hypotension or bradycardia before cardiopulmonary bypass Hypotension after bypass was no more common in patients off propranolol 12 to 48 hours than in patients who either discontinued the drug over 48 hours before operation or had never taken the drug The operative mortality rate was 4% in patients taking propranolol within 48 hours of surgery and 6% in all other patients The authors concluded that propranolol could be safely given within 12 to 48 hours of coronary artery surgery

Kaplan and Dunbar[1] in 1976 also showed that patients with angina pectoris undergoing noncardiac surgical procedures and general anesthesia could safely tolerate propranolol administration to within 24 hours of operation

The relative safety of maintaining propranolol just prior to surgery established by these retro

spective studies emphasized the need for a prospective study to delineate the true clinical interaction between propranolol and general anesthesia for coronary artery operations[9] Reports associating the abrupt withdrawal of long term propranolol therapy with an increase in angina pectoris new arrhythmias myocardial infarction or sudden death raised the issue as to whether the risk of such withdrawal before coronary bypass operation was greater than the risk of purported myocardial depression[7, 9]

The mechanism for the withdrawal reaction is unknown but since propranolol lowers myocardial oxygen requirements abrupt withdrawal of the drug may then raise the oxygen requirements beyond what the coronary arteries can supply resulting in severe ischemia or myocardial infarction[2] Other postulated mechanisms include increased platelet aggregability[28] hypersensitivity to circulating catecholamines (analagous to denervation hypersensitivity)[29] and reactivation of the renin angiotensin aldosterone mechanism[6]

In a recent editorial Shand and Wood[26] felt that the propranolol withdrawal syndrome was real but rare Shiroff and associates[30] found the syndrome to be rare in patients with angina pectoris who had their propranolol stopped abruptly prior to cardiac catheterization The effect may have been blunted in Shiroff's series because these patients had reduced in hospital physical activity However a rebound effect following propranolol withdrawal may be more important in the setting of surgical stress There is evidence that catecholamines and the level of adrenergic tone are elevated during laryngoscopy and intubation[3, 3] and again after saphenous vein coronary bypass[6, 3, 18] There are marked increments in blood pressure demonstrated during intubation and a marked increase in heart rate blood pressure and arrhythmias in the immediate postoperative state[3] Patients who have their propranolol stopped abruptly may become hypersensitive to catecholamines during these periods

In a retrospective study by Langou and co workers the risk of perioperative myocardial infarction was significantly increased by abrupt propranolol withdrawal 24 hours before coronary surgery compared to a gradual withdrawal regimen (32% infarct rate vs 7 3 infarct rate)

Recent studies by Kirsh and associates Kopriva and colleagues[14] and Boudoulas and co workers[16] demonstrated the safety of propranolol administered within 1 to 5 hours of coronary artery surgery

In a large prospective trial by Slogoff and associates[4] chronic propranolol therapy was administered in full dosage just prior to surgery and comparison was made with groups of patients where therapy was not given or where it was abruptly withdrawn 24 to 72 hours preoperatively Patients abruptly withdrawn from their propranolol treatment had the highest incidence of intraoperative ischemia and arrhythmias probably related to a higher rate pressure product than was seen in patients where propranolol was maintained just prior to surgery Hypotension and bradycardia were not more common in patients who had propranolol continued Moreover no differences among groups were noted in ease of discontinuation of cardiopulmonary bypass need for cardiac stimulants or in mortality rate

In another recent prospective study Boudoulas and colleagues[3] demonstrated that propranolol maintained prior to surgery in patients lowered the incidence of supraventricular tachyarrhythmias in the postoperative period when compared to patients where propranolol was abruptly discontinued 24 hours prior to surgery There were no complications related to propranolol during the intraoperative period The left ventricular function as measured from systolic time intervals was the same pre and postoperatively with both treatment regimens

Our group demonstrated a high incidence of supraventricular arrhythmias and hypertension following coronary artery bypass in patients with angina pectoris who had propranolol withdrawn greater than 48 hours prior to surgery when compared to patients who had the drug maintained just prior to surgery[18] We postulated a propranolol withdrawal effect as the cause for these phenomena and carried out a trial described in this report using different preoperative propranolol treatment regimens with comparisons made with patients receiving no previous propranolol therapy

The results of this study show that propranolol can be given safely to hemodynamically stable patients just before they undergo elective coronary artery bypass surgery Propranolol treated patients (group IV—drug maintained just prior to surgery and restarted postoperatively) had a sig

nificant blunting of the hypertensive reflex usually seen during intubation[31] and demonstrated negligible changes in the rate pressure product in the postoperative period A significant reduction in the incidence of supraventricular arrhythmias was also noted Of concern was the finding that there were greater increments in systolic blood pressure and rate pressure product during the intubation and postoperative periods in those patients where propranolol was stopped 10 to 48 hours prior to surgery (groups II III) when compared to group I (no propranolol) and group IV patients There was also a significantly higher incidence of arrhythmias seen in those patients who had propranolol abruptly withdrawn compared to group IV patients

The data in this report suggest that there is a true propranolol withdrawal effect which becomes manifest during coronary artery surgery This phenomenon does not appear to be mediated through the renin angiotensin system as was previously suggested[30-3] but probably by a hyperadrenergic response to a stress situation The patients who never received propranolol did not demonstrate a large increment in rate pressure product in the postoperative period despite having higher serum renin activity when compared to group IV patients (propranolol maintained) The marked increments in rate-pressure product (an indirect index of myocardial oxygen demand) and frequency of arrhythmia in the postoperative periods was a specific finding in those patients who had propranolol abruptly withdrawn *Patients who had propranolol main*tained just prior to surgery (group IV) failed to demonstrate this postoperative rate pressure product of arrhythmia increment Catecholamines were not measured so it is not exactly known whether the postoperative rate pressure product increments in this study are secondary as suggested by others to increased catecholamine levels adrenoceptor hypersensitivity or both

In this study the finding that those patients who had propranolol stopped just 10 hours prior to surgery and were not protected from marked increments in rate pressure product during the operative (intubation) and postoperative period was surprising in light of the alleged prolonged pharmacodynamic half life of propranolol which contrasts to its shorter pharmacokinetic half life[33] This might be explained by the increased clearance of the drug during cardiopulmonary bypass and the heightened adrenergic state in the immediate postoperative period Negligible plasma drug levels were found following cardiopulmonary bypass in both group III and IV patients reinforcing a need to maintain propranolol intravenously in the immediate postoperative period to protect against the postoperative hyper adrenergic state[3-41]

There are important clinical implications of this study First increased myocardial oxygen demands during intubation may be even more important than a compromised blood supply in causing ischemia The finding of intubation induced hypertension and tachycardia has been demonstrated in many studies, which emphasizes the need to protect patients with beta adrenergic blockade from this catecholamine-mediated phenomenon[31] Moreover a propranolol withdrawal effect following abrupt premature discontinuation of the drug may further aggravate this phenomenon Many of the perioperative myocardial infarctions which have been observed with coronary bypass surgery[34] may relate to the intubation related increase in rate-pressure product an effect which usually persists for five minutes[2] In this study five myocardial infarctions were seen in group II and group III patients vs none in group IV patients

Secondly there is probably no need to give propranolol during the operative period Halothane and enflurane are the general anesthetics most commonly used for coronary artery bypass *surgery and like propranolol, are myocardial* depressants (agents that will lower the oxygen demand of the heart)[7] These anesthetic drugs have been shown to decrease the activity of the sympathetic nervous system and to reduce the output of catecholamines by adrenergic nerve endings and the adrenal medulla Direct effects on autonomic nerve terminals have not been demonstrated and there is no reason to believe nor any evidence to support the notion that halothane may act on adrenal receptors[3] As demonstrated in this report patients in all four groups had similar low rate-pressure products after one hour of halothane anesthesia The effects of propranolol and halothane are usually additive and not potentiated with the concentrations of halothane used in coronary artery surgery

Thirdly the well-documented hyperadrenergic state in the early postoperative period[3-4] may

explain the high incidence of hypertension and arrhythmias reported in this study[37-41] Maintenance propranolol given intravenously appears to blunt this stress reaction whereas premature propranolol withdrawal seems to aggravate it The supraventricular arrhythmias appear to be catecholamine mediated since they all respond to intravenous propranolol therapy Unlike propranolol the efficacy of digoxin in treating post operative arrhythmias has not been demonstrated[59]

Maintenance of myocardial oxygen demands at relatively low levels with propranolol might be especially important in the pre bypass operative period for patients undergoing complete coronary artery revascularization The demonstration that perioperative myocardial infarction often occurs in the period between anesthesia induction and onset of cardiopulmonary bypass emphasizes the need for myocardial protection during this most vulnerable period[60 61] In the post bypass period myocardial oxygen demands should also be controlled especially in those patients who undergo incomplete coronary revascularization procedures where threatened myocardium may still remain or in non cardiac operative procedures for patients with angina pectoris where the entire myocardium may remain threatened

The mortality rate of patients with angina pectoris undergoing elective non cardiac procedures has been reported to be three times higher than that of patients undergoing elective coronary revascularization procedures[62] Proper anesthetic technique and careful hemodynamic monitoring are important for all patients with ischemic coronary artery disease who undergo either non cardiac or cardiac operations In this study all the perioperative myocardial infarctions were seen in those patients who either had propranolol abruptly withdrawn or who never received the drug preoperatively

Many of the newer beta adrenoceptor blocking agents (i e practolol cardioselective pindolol intrinsic sympathomimetic activity alprenolol labetalol alpha and beta blocking activity) have been evaluated during surgical procedures and like propranolol were found to be well tolerated[33 43] Since all the beta adrenoceptor blocking agents have similar effects on angina pectoris arrhythmia and hypertension the danger of abrupt treatment withdrawal with these agents should parallel that seen with propranolol

Conclusions

1 Propranolol can safely be maintained just prior to coronary artery surgery in hemodynamically stable patients and can be safely resumed in the immediate postoperative period with no difficulty

2 Propranolol blunts the profound increases in myocardial oxygen demand seen during intubation and postoperative periods These increments appear to be catecholamine mediated and are unrelated to the renin angiotensin system

3 There is a demonstrable propranolol withdrawal effect when the drug is abruptly stopped 10 to 48 hours prior to coronary artery surgery which appears to aggravate the hyperadrenergic state seen during the intubation and postoperative periods

4 There is a rapid clearance of propranolol during cardiopulmonary bypass with disappearance of the drug demonstrating the need to temporarily re start the drug in the immediate postoperative period where adrenergic tone is high

5 There is a high incidence of supraventricular arrhythmias seen in patients where propranolol is abruptly withdrawn 10 to 48 hours prior to surgery The arrhythmias are probably catecholamine mediated since they are prevented by propranolol prophylaxis and respond readily to treatment with propranolol

6 The recognition of a propranolol withdrawal effect during cardiac surgery raises an even greater concern for those patients with chronic angina pectoris who are receiving propranolol prior to undergoing non cardiac surgical procedures and where the drug is abruptly stopped

Recommendations We strongly believe that with the proper indications for its use chronic therapy with propranolol should be continued in moderate doses to the time of surgery (we recommend half the usual dose be given orally 2 hours prior to surgery and restarting intravenous propranolol immediately postoperatively) Not only will this minimize the occurrence of complications of the patient s disease in the preoperative period but cardiovascular stability may actually be improved by the persistence of propranolol effects during anesthesia The lower heart rate and blood pressure are favorable for minimizing myocardial oxygen demands and the incidence and severity of episodes of tachycardia and dysrhythmias are probably less in patients main

tained on beta blockers up to the time of surgery

Propranolol should not be abruptly withdrawn even as early as 10 hours prior to surgery The question of gradual withdrawal of therapy prior to surgery has not been well resolved but in the absence of apparent complications from continued propranolol therapy there is little justification for even gradual withdrawal

Summary

In an attempt to resolve the controversy concerning propranolol therapy in patients undergoing coronary artery revascularization surgery 54 consecutive patients with stable angina pectoris receiving chronic propranolol therapy entered a randomized trial and were compared with 17 patients on no propranolol therapy (group I) The 54 patients were divided into three treatment groups in group II (n = 17) propranolol was abruptly withdrawn 48 hours prior to surgery in group III (n = 18) propranolol was abruptly withdrawn 10 hours prior to surgery in group IV (n = 19) propranolol was maintained until the day of surgery half the usual dose was given 2 hours prior to surgery and intravenous propranolol was administered every four hours postoperatively Patients in group II and III had significantly higher increases in the rate pressure product (RPP) during intubation and in the postoperative periods compared to patients in groups I and IV Group IV had the lowest increase in RPP during intubation and a significantly lower incidence of postoperative supraventricular arrhythmias Patients abruptly withdrawn from propranolol at 10 or 48 hours preoperatively are more prone to increments in myocardial oxygen demands than those patients not treated with propranolol postoperatively or who were maintained on the drug Plasma renin activity although lower in patients treated with propranolol (group IV) did not seem to play a role in the RPP increments seen The increased sympathetic tone associated with intubation and the postoperative period most likely contribute to the increments in RPP and the increased incidence of arrhythmia These data show that (1) propranolol may be given safely to patients at the time of coronary artery bypass and may be maintained postoperatively without a decrement in left ventricular performance (2) there is a rebound effect or increased sympathetic activity in patients who have propranolol abruptly withdrawn 10 or 48 hours prior to surgery This rebound effect causes a marked increase in myocardial oxygen demands during intubation and the postoperative periods with an increased incidence of arrhythmias (3) Continuous propranolol treatment up until the time of surgery with maintenance of intravenous therapy in the immediate postoperative period provides protection against these complications (4) The data and implications can reasonably be expected to apply to propranolol treated patients with angina pectoris undergoing general anesthesia and noncardiac surgical procedures

REFERENCES

1 Frishman W and Silverman R Clinical pharmacology of the new beta adrenergic blocking drugs. Part 3 Comparative clinical experience and new therapeutic applications, AM HEART J 98 119 1979
2. Viljoen J F Estafanous F G and Kellner G A Propranolol and cardiac surgery J Thorac Cardiovasc Surg 64 8 6 1972.
3. Boudoulas H Lewis, R P Snyder G L. Karayannacos P and Vasko J S Beneficial effect of continuation of propranolol through coronary bypass surgery Clin Cardiol 2 87 1979
4 Slogoff S Keats A S and Ott E Preoperative propranolol therapy and aortocoronary bypass operation J.A M.A 240 1487 1978
5 Kirsh M M Behrendt D M Jackson A P Dhadphale P Alsen S Brymer J Orringer M B and Sloan H Myocardial revascularization in patients receiving long term propranolol therapy Ann Thorac Surg 25 117 1978
6 Romagnoli, A and Keats, A S Plasma and atrial propranolol after preoperative withdrawal Circulation 52 1123 1975
7 Alderman E L Coltart D J Wettach G E and Harrison D C Coronary artery syndromes after sudden propranolol withdrawal Ann Intern Med 81 625 1974
8 Miller R R Olson H G Amsterdam E A and Mason D T Propranolol withdrawal rebound phenomenon Exacerbation of coronary events after abrupt cessation of antianginal therapy N Engl J Med 293 416 1975
9 Shand D G Propranolol withdrawal N Engl J Med 293 449 1975
10 Caralps J M Mulet J Wienke H R Moran J M and Pifarre R Results of coronary artery surgery in patients receiving propranolol J Thorac Cardiovasc Surg 67 526 1974
11 Moran J M Mulet J Caralps, J M and Pifarré R Coronary revascularization in patients receiving propranolol, Circulation 49 and 50 (Suppl II) II 116 1974
12. Kaplan J A. and Dunbar R W Propranolol and surgical anesthesia Anesth Analg 55 1 1976
13 Kopriva C J Guinazu A and Barash P G Massive propranolol therapy and uncomplicated cardiac surgery J.A M A 239 1157 1978
14 Kopriva C J Brown A C D and Pappas G Hemodynamics during general anesthesia in patients receiving propranolol Anesthesiology 48 28 1978

15 Jones E L Kaplan J A Dorney E R King S B Douglas J S and Hatcher C R Propranolol therapy in patients undergoing myocardial revascularization Am J Cardiol 38 696 1976

16 Boudoulas H Snyder G L Lewis R P Kates R E Karayannacos P E and Vasko J S Safety and efficacy of continued propranolol administration through coronary bypass surgery (Abstract) Am J Cardiol 41 369 1978

17 Kaplan J A Dunbar R W Bland J W Sumpter R and Jones E L Propranolol and cardiac surgery a problem for the anesthesiologist Anesth Analg 54 571 1975

18 Salazar C Frishman W Friedman S Patel J Lin Y Oka Y Frater R W M and Becker R β blockade for supraventricular tachycardia post coronary artery surgery a propranolol withdrawal syndrome Angiology (In press)

19 Robinson B F Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris Circulation 35 1072 1967

20 Nelson R R Gobel F L Jorgenson C R Wang K Wang Y and Taylor H L hemodynamic predictors of myocardial oxygen consumption during static and dynamic exercise Circulation 50 1179 1974

21 Coltart D J and Shand D G Plasma propranolol levels in the quantitative assessment of β adrenergic blockade in man Br Med J 3 731 1970

Chervu L R Lory M Liang T Lee H B and Blaufox M D Determination of plasma renin activity by radioimmunoassay Comparison of results from two commercial kits with bioassay J Nucl Med 13 806 1972

23 Powell C E and Slater I H Blocking of inhibitory adrenergic receptors by a dichloro analog of isoproterenol J Pharmacol Exp Ther 122 480 1958

24 Johnstone M Propranolol during halothane anaesthesia Br J Anaesth 38 516 1966

25 Faulkner S L Hopkins J T Boerth R C Young J L Jellett L B Nies A S Bender H W and Shand D G Time required for complete recovery from chronic propranolol therapy N Engl J Med 289 607 1973

26 Shand D G and Wood A J J Editorial Propranolol withdrawal syndrome—why? Circulation 58 202 1978

Frishman W Silverman R Strom J Elkayam U Weinstein J and Sonnenblick E Clinical pharmacology of the new beta adrenergic blocking drugs Part 4 Adverse effects Choosing a β adrenoceptor blocker AM HEART J 98 2[illegible] 19[illegible]

28 Frishman W H Christodoulou J Weksler B Smithen C Killip T and Scheidt S Abrupt propranolol withdrawal in angina pectoris Effects on platelet aggregation and exercise tolerance AM HEART J 9[illegible] 169 19[illegible]8

29 Boudoulas H Lewis R P Kates R E and Dalamangas G Hypersensitivity to adrenergic stimulation after propranolol withdrawal in normal subjects Ann Intern Med 87 43[illegible] 1[illegible]

30 Shiroff R A Mathis J Zelis R Schneck D W Babb J D Leaman D M and Hayes A H Propranolol rebound—a retrospective study Am J Cardiol 41 778 1978

31 Tomori Z and Widdicombe J G Muscular bronchomotor and cardiovascular reflexes elicited by mechanical stimulation of the respiratory tract J Physiol (Lond) 200 2[illegible] 1[illegible]

Prys Roberts C Greene L T Meloche R and Foex P Studies of anaesthesia in relation to hypertension II Haemodynamic consequences of induction and endotracheal intubation Br J Anaesth 43 531 1971

33 Prys Roberts C Foex P Biro G P and Roberts J G Studies of anaesthesia in relation to hypertension V Adrenergic beta receptor blockade Br J Anaesth 45 671 1973

34 Stoelting R K and Peterson C Circulatory changes in patients with coronary artery disease following thiamylal succinylcholine and tracheal intubation Anesth Analg 55 232 1976

35 DeVault M Greifenstein F E and Hayes L C Circulatory responses to endotracheal intubation in light general anesthesia—the effect of atropine and phentolamine Anesthesiology 21 360 1960

36 Bassell G M Lin Y T Oka Y Becker P M and Frater R W M Circulatory response to tracheal intubation in patients with coronary artery disease and valvular disease Bull N Y Acad Med 54 84? 19[illegible]8

37 Boudoulas H Lewis R P Vasko J S Karayannacos P E and Beaver B M Left ventricular function and adrenergic hyperactivity before and after saphenous vein bypass Circulation 53 802 1976

38 Wallen J L Kaplan J A and Jones E L Anesthesia for coronary revascularization *in* Cardiac Anesthesia Kaplan J ed New York 1979 Grune & Stratton Inc pp 270-271

39 Whelton P K Flaherty J T MacAllister N P Watkins L Potter A Johnson D Russell R P and Walker W G Hypertension following coronary artery bypass surgery the role of preoperative propranolol therapy (Abstract) Am J Cardiol 43 4?? 1979

40 Goldstein R Corash L Tallman J Lake R Hyde J Anderson J and Epstein S Decrease in platelet survival and enhancement of sympathetically mediated reflex rises in heart rate after abrupt withdrawal of propranolol (Abstract) Am J cardiol 43 416 1979

41 Bernstein V and Miyagishima R T Rapid beta blockade for control of atrial arrhythmias following coronary bypass surgery (Abstract) Ann R Coll Phys Surg Canada 11 33 1978

42 Roberts A J Niarchos A P Subramanian V A Abel R M Herman S D Sealey J E Case D B White R I Johnson G A Laragh J H and Gay W A Systemic hypertension associated with coronary artery bypass surgery predisposing factors hemodynamic characteristics humoral profile and treatment J Thorac Cardiovasc Surg 74 846 1977

43 Hine I P Wood W G Mainwaring B Butler M J Irving M H and Booker B The adrenergic response to surgery involving cardiopulmonary bypass as measured by plasma and urinary catecholamine concentration Br J Anaesth 48 355 1976

44 Barta E Kuzela L Kvetnansky R Siska K Faltusova F Torda M Cornak V and Horecky J Activity of sympathetic nerves in heart during cardiopulmonary bypass in patients J Cardiovasc Surg 17 174 1976

45 Tan C K Glisson S N El Etr A A and Ramakrishnaiah K B Levels of circulating norepinephrine and epinephrine before during and after cardiopulmonary bypass in man J Thorac Cardiovasc Surg 71 928 1976

46 Fratilas V Vlachakis N D and Pitwak R Hypertension and plasma catecholamines following aortocoronary bypass surgery (Abstr) Clin Res 25 [illegible] 1977

47 Fouad F M Estafanous F G and Tarazi R C Hemodynamics of postmyocardial revascularization hypertension Am J Cardiol 41 564 1978

48. Wallach R Karp R B Reves I G Oparil S and James T N Mechanism of hypertension after saphenous vein bypass surgery (Abstr) Circulation 55 and 56 (Suppl III) III 141 1977
49. Langou R A Wiles J C Peduzzi I N Hammond C L and Cohen L S Incidence and mortality of perioperative myocardial infarction in patients undergoing coronary artery bypass grafting Circulation (Suppl II) 56 II 54 1977
50. Taylor K M Morton I J Brown J J Bain W H and Caves P K Hypertension and the renin angiotensin system following open heart surgery J Thorac Cardiovasc Surg 74 839 1977
51. Niarchos A P, Roberts A J Case D Gay W A and Laragh J H Hemodynamic characteristics of hypertension after coronary bypass surgery and effects of the converting enzyme inhibitor Am J Cardiol 43 586 1979
52. *Wilson M Morgan G, and Morgan T The effect of* blood pressure of β adrenoceptor blocking drugs given once daily Clin Sci Mol Med. 51 277 1976
53. Boudoulas H Beaver B M Kates R E and Lewis R P, Pharmacodynamics of inotropic and chronotropic responses to oral therapy with propranolol Chest 73 146 1978
54. Frishman W Clinical pharmacology of the new beta adrenergic blocking drugs Part 1 Pharmacodynamic and pharmacokinetic properties AM HEART J 97 663 1979
55. Shand D G Pharmacokinetics of propranolol a review Postgrad Med J 52(Suppl 4) 22 1976
56. Bristow J O A cardiologist s view of coronary bypass surgery *in* Progress in Cardiology Vol 6 Yu P N and Goodwin J F, eds Philadelphia 19 Lea & Febiger pp 28-79
57. Hug C C Pharmacology—anesthetic drugs *in* Cardiac Anesthesia Kaplan J ed New York 1979 Grune & Stratton Inc pp 7 13
58. Slogoff S Keats A S Hibbs C W Edmonds C H and Bragg D A Failure of general anesthesia to potentiate propranolol activity Anesthesiology 47 504 1977
59. Tyras D H Stothert J C Kaiser G C Barner H B Codd J E and Willman V I Supraventricular tachyarrhythmias after myocardial revascularization a randomized trial of prophylactic digitalization J Thorac Cardiovasc Surg 77 310 1979
60. Isom O W Spencer F C Feigenbaum H Cunningham J and Roe C Pre bypass myocardial damage in patients undergoing coronary revascularization an unrecognized vulnerable period (Abstr) Circulation 52 (Suppl II) 119 1975
61. Delva F Maillé J G Solymoss B C Chabot M Crondin C M and Bourassa M C Evaluation of myocardial damage during coronary artery grafting with serial determinations of serum CPK MB isoenzyme J Thorac Cardiovasc Surg 75 467 1978
62. Logue R B and Kaplan J A Medical management in non cardiac surgery *in* The Heart Hurst J W editor New York 1978 McGraw Hill p 1 6
63. Scott D B Buckley F P Drummond C B Littlewood D G *and MacRae W R Cardiovascular effects* of labetalol during halothane anaesthesia Br J Clin Pharmacol (Suppl 3) 817 1976
64. Brichard G Practolol in anesthesia Acta Cardiol (Brux) Suppl 16 119 1972
65. Malcolm Thomas B and Rolly G Preliminary report on the use of practolol in anaesthesia Acta Cardiol (Brux) Suppl 16 10 1972
66. Yoshikawa K, Tosaki Y and Yoshiya I Use of LB 46 a new anti arrhythmic agent during anesthesia Med J Osaka Univ 23 189 19
67. Nichola G Nicholas F and Rozo L Problem posed by anesthesia in the hypertensive treated with beta blockers Arch Mal Coeur 69 1311 1976
68. Erding L Nalbantgil E Kiliccioglu B Nalbantgil I and Yidinel I Prevention by pindolol of electrocardiographic changes during bronchoscopy performed under local and general anesthesia Ann Anesthesiol Fr 18 747 1977
69. Frishman W and Silverman R Clinical pharmacology of the new beta adrenergic blocking drugs Part 2 Physiologic and metabolic effects AM HEART J 9 79 1979

Annotations

Measuring ventricular function after coronary bypass surgery

From the onset of the coronary bypass operation clinical investigators have reported improvement of ventricular function following operation with the conclusion that the observed changes were the result of the specific effect of the operation Studies of exercise capability and more recently studies using sophisticated radionuclide techniques of measuring ventricular function have demonstrated with "statistical significance" an improvement following coronary bypass Although most clinicians find an immediate and seemingly rational causal correlation between the operation and subsequent ventricular improvement, fitting with prior "clinical judgment" this correlation with its attendant conclusion is an unproven hypothesis It may well be correct but needs testing lest it be wrong and lead to false conclusions. The conclusion that the operation is responsible for improvement rests on the exclusion of other factors that may also result in improvement For centuries, clinicians initially have alleged benefit from almost all therapeutic innovations because of the association of patient improvement following the therapy It is not enough to observe that patients improve following therapy—that happens with most therapies and often without or in spite of therapy It is an anachronism of the clinical investigation paradigm that there often is no scientific testing to determine the specific factor responsible for improvement following therapy

There has always been a tendency for clinicians to mistakenly equate objectivity of assessment with objective measurements. If a biological function can be measured by objective standards, such as weight length, time or ejection fraction the majority of clinicians assume that assessments based on such measurements are "objective" For example it was alleged that because patients could walk up and down more steps following the Beck operation as compared to before the operation that this constituted "objective" evidence of improvement due to the operation Although the measurements of steps were objective and no doubt accurate the assessment was not objective because no attention was paid to the many other factors that were involved in the longer exercise performance of those patients

In addition to the specific effect of coronary bypass surgery there are many other factors that may possibly contribute to or explain improvement in ventricular function Those of which we are aware include the following

1 The regression effect is usually overlooked in assessment of therapy Patients who have chronic illnesses go through cycles of variation [illegible] They are much more likely to seek medical help and the physician is much more likely to [illegible] during clinical relapses [illegible] bypass surgery [illegible] clinical relapse or at the [illegible] and it is [illegible] possible that many patients [illegible] therapy would otherwise have improved spontaneously [illegible] function likely will improve spontaneously following periods of increased ischemia and attribution of improvement to an intervening therapy may be incorrect Failure to account for this phenomenon produces an unwarranted bias in assessment of the therapy

2 Patients receiving coronary bypass surgery almost always have a profound belief that this therapy is protective against myocardial infarction or death and many look upon the treatment as curative It is axiomatic that psychological factors influence physiologic functioning, and although we know very little about quantification of such factors it is clear that psychological factors are very important in exercise test results, and it is possible that they play a role in exercise ventricular function as well. Certainly any therapy that reduces anxiety as does coronary bypass surgery will produce profound symptomatic improvement on that basis alone This fact is virtually never accounted for in evaluation of symptomatic results of bypass surgery The non-specific effects of major surgical therapy are well demonstrated in patients with unsuccessful bypass operations (all grafts occluded) most of whom have improved ventricular function after operation Patients who received the Beck internal mammary artery ligation and Vineberg operation also had improved ventricular function Proper evaluation of bypass surgery must account for this important factor

3 Physical conditioning is capable of improving ventricular function in patients with severe coronary artery disease even to the extent of reversing or eliminating decreased ejection fraction with exercise If patients who have had coronary bypass surgery feel that they are sufficiently protected that they can embark upon exercise conditioning programs as is encouraged this factor alone could improve ventricular function as compared to medically treated patients who do not change their life styles Even though increased physical conditioning may be secondary to a psychological sp[illegible] effect of surgery (as may be the case with cessation of smoking also) these are non-specific effects of the therapy and should be recognized as such. It is inaccurate and potentially misleading to assess bypass surgery without accounting for exercise conditioning before and during the evaluation period.

4 Perhaps the most important determinant of observed differences of ventricular function comparing operated and non-operated patients, is an inherent difference between the treatment and control groups If the control group of patients is not selected by the same criteria used for selection of patients for coronary bypass surgery the groups will be inherently different Therefore observed differences noted at a later date due to different prognoses of the groups are not only possible but expected There is much evidence that patients selected for coronary bypass surgery are inherently different from those selected not to have surgery When surgical patients are compared to non surgical patients, [illegible]

0002-8703/80/020270 + 02$00.20/0 © 1980 The C. V. Mosby Co

most cases the comparison is invalid regardless of statistical analysis because of the inherent differences between the groups The great majority of all studies of ventricular function following coronary bypass surgery suffer from this deficiency

Another possible influencing factor well known but usually unheeded is the natural bias of investigators who have an interest in the outcome of studies Quite aside from personal integrity if one stands to gain from a particular observation the likelihood of making that observation is enhanced Clinical investigation is one of the few spheres of testing in which assessments are made by those who have a direct and personal interest in the outcome rather than by unbiased independent investigators

The basic fallacy in most studies of ventricular function is the failure to provide an adequate control group Proper controls do not ensure that the two groups are absolutely equal, and they are sometimes very difficult to obtain but without a valid control group for comparison there is no way to isolate the specific effect of the treatment under study from the many other factors that may influence the end result It is far better that we utilize scientific methods even if it means that we must profess uncertainty about the causal relationship of therapy and observed changes than to deceive ourselves with uncontrolled studies that lead to false conclusions. In disdain of adequate controls, most clinical investigations provide a parody of scientific analysis and produce belief of unsupported hypotheses that frequently perpetuate worthless concepts or therapies.

Coronary bypass surgery may well improve left ventricular function or it may not the studies to date are insufficient to provide accurate information It is scientifically unacceptable to conclude that bypass surgery is the specific cause of ventricular functional improvement when so many other factors that can explain the observation are not even considered We must be willing to say that although ventricular function appears to improve following bypass surgery we do not know what proportion if any of that improvement is due to the operation Until we learn to admit of our lack of knowledge and adopt methods that are more accurate we will be bereft of that knowledge that we so forcefully proclaim.

Thomas A Preston M.D
University of Washington
School of Medicine
Seattle
U S Public Health Service Hospital
P O Box 3145
Seattle Wash 98114

REFERENCES

1 Kent K M Borer J S., Green M V Bacharach S L. McIntosh C L. Conkle D M., and Epstein S E Effects of coronary artery bypass on global and regional left ventricular function during exercise N Engl J Med **298** 1434 1978
2 Feil H Clinical appraisal of the Beck operation Ann Surg **118** 807 1943
3 Block T A Murray J S., and English, M T Improvement in exercise performance after unsuccessful myocardial revascularization, Am. J Cardiol. **40** 673 1977
4 Preston T A. Coronary Artery Surgery A Critical Review New York 1977 Raven Press, Chapter 2
5 Wallace A G Rerych S K., Jones R H and Goodrich, J K Effects of exercise training on ventricular function in coronary disease Circulation **58** 11 1978
6 Plotnick G D., and Conti, C R Unstable angina Angiography short and long term morbidity mortality and symptomatic status of medically treated patients Am. J Med **63** 870 1977
7 Gross H Vaid A K., and Cohen, M V Prognosis in patients rejected for coronary revascularization surgery Am. J Med. **64** 9 1978

The risks of intestinal bypass operations

Recently it has been determined that a 35 to 45-year old man with a weight excess of 100 pounds is ten to eleven times more likely to die than his normal weight counterpart Most deaths were related to cardiovascular disease Medical measures to produce weight loss had been notoriously unsuccessful justifying surgical approaches which promised lasting improvement However before recommending any of the various surgical procedures to treat obesity the limitations and hazards should be well understood

The intestinal bypass has enjoyed increasing popularity and is still the most widely used operation Interestingly the first patient so treated by Dr Kremen in Minneapolis is still alive 24 years later but has had a coronary occlusion—despite normal weight This brings up the first question. Does the drastic decrease in serum triglyceride and cholesterol levels following this procedure prevent ischemic heart disease? There is evidence that HDL concentrations diminish as well and cholesterol content of arterial tissue actually rises Thus the lowering of blood lipids may not result in lessened atherogenesis.

Admittedly in addition to weight loss there are health benefits Blood pressure is lowered Blood sugar if elevated becomes normal in most patients Pickwickian patients improve and the hazard of pulmonary embolism is lessened. However actuarial data on the survival of bypass patients have not been published. Thus we don t know if this group will live longer than untreated obese subjects, but it has become abundantly clear that the intestinal bypass only rarely achieves normal weight plus good health. Obesity with its handicaps was traded off against a multitude of minor and major acute or chronic complications.

The long excluded bowel segment is equivalent to a huge blind loop and all the manifestations of a blind loop syndrome can be anticipated Arthritis, vasculitis in various forms, skin lesions, and neurological defects have been described. Progressive damage involving the liver or the kidneys may occur

0002-8 03/80/020_71 + 02$00 20/0

without subjective symptoms or clinically recognizable manifestations. Only sequential liver biopsies will reveal worsening fibrosis but cirrhosis can be prevented by timely dismantling of the bypass. Damage to the kidneys is a much more problematic and treacherous complication. Biopsies had demonstrated extensive structural changes while kidney function tests had remained entirely normal. At least two mechanisms can cause renal injury. First, nearly all bypass patients develop hyperoxaluria and in close to half the patients oxalate crystals are deposited in tubules, causing focal lesions fibrosis and atrophy. The incidence of severe renal oxalosis is unknown. The rate of progression can be highly variable. Irreversible renal failure has occurred as early as three months, and as late as seven years after the operation.

Second, injurious immune complexes, related to bacterial overgrowth in the bypassed bowel, have been found to cause a glomerulopathy independent of the oxalate induced damage. The clinical course of this type of interstitial nephritis has not been defined, but there are indications that functional impairment may ensue through this mechanism as well. The morphological picture ranges from a granulomatous nephritis to glomerular pathology indistinguishable from disseminated lupus erythematosus. While hepatic failure may be preventable with proper treatment, there is no evidence that the renal injury is avoidable. The great majority of bypass patients studied had variable degrees of renal damage.

There may be in excess of 80 000 bypass patients in the United States. The over all complication rate has been high and several large centers have concluded that intestinal bypass operations are no longer a viable treatment modality. In fact it would seem reasonable to advise bypass patients of the possible long range hazards. The suggestion might be made that the bypass can be dismantled and that a gastroplasty or gastric exclusion operation could be substituted in order to prevent recurrent weight gain. These operations are considerably safer since mechanical interference with food intake is the only effect.

Ernst J Drenick MD
Chief General Medicine
Wadsworth VA Hospital Medical Center
Professor in Residence
Department of Medicine
UCLA School of Medicine
Los Angeles Calif 9[illegible]

REFERENCES

1. Kral, J. G., and Bondjers, G. Increased arterial tissue cholesterol after intestinal bypass in severe obesity. Lancet 288-289 August 5 19[illegible]8
2. Drenick, E. J., Ament, M. E., Finegold, S. M. Corrodi, P. and Passaro E. Bypass enteropathy. Intestinal and systemic manifestations following small bowel bypass. J.A.M.A. 236 269 1976
3. Drenick, E. J., Stanley T. M., Border W. A., Zawada, E. T., Dornfeld L. P., Upham, T., and Llach, F. Renal damage after intestinal bypass. (Part I) Ann. Intern. Med. 89 594 1978

Doctors drugs and compliance

As internists our major therapeutic approach to patients medical problems is the use of drugs. The success of our efforts is heavily dependent on the efficacy of the agents effective prescribing of drugs, the compliance of the patient in taking the drug and the avoidance of adverse drug reactions. It should therefore be evident that to evaluate the success or failure of a drug regimen one must know certain basic information: the name of the drug used, the dosage and directions given to the patient and the names of other drugs being given concomitantly. In private practice settings such information may be remembered between visits by the practitioner. Where multiple providers are caring for the same patient as in group practices or hospital based programs the major means of communication of such information is the medical record.

In a recent study the medical records of [illegible] patients followed in a hospital based outpatient program were examined to determine if information relating to drugs was adequately documented. To do this investigators independently reviewed the medical record and the prescription files of drugs actually dispensed to the patient. The medical record could then be evaluated for completeness and accuracy of drug names, dosage and directions. Th[illegible] was a discrepancy between the pharmacy files of drugs dispensed and the medical chart in one or more of these items in [illegible] of the records. Drugs with a narrow therapeutic range such as anticoagulants digoxin antiarrhythmic, or chemotherapeutic agents, were no more accurately documented than were other agents. Where two or more drugs with a potential for significant drug interaction were being administered one of these drugs was not named in the chart in 6[illegible] of the cases. For [illegible] of the patients receiving Warfarin and a potentially interacting drug the chart failed to document one of the drugs. Forty three patients received two or more drugs of the same therapeutic type including analgesics sedatives, and diuretics. These duplications were not evident in the chart in 3[illegible] instances ([illegible]).

When we assess the outcome of medical care provided in this country we can no longer tout our advanced technology as a guarantee of success. The literature reveals that even common medical problems such as hypertension are frequently poorly managed and have unacceptable outcomes. If we are to make a significant impact on the health of a large number of patients by our interventions, we must correctly identify the health problem implement an appropriate therapeutic regimen and monitor the results of such therapy. The problem of patient compliance has received increasing amounts of attention. A variety of approaches have been tried

0002-8703 80 020272 + 0[illegible]00 20/0 © 19[illegible]0 The C. V. Mosby Co

improve patient compliance in drug therapy by interven of physicians, nurses, pharmacists, and other trained rsonnel Many of these interventions are associated with ement but often compliance returns to pre-interven *level upon withdrawal of the program*

Beneficial outcomes of therapy however depend not only n patient compliance but also on rational drug use and dance of adverse drug reactions and interactions whenev possible This "physician compliance" has received far less tion and is most often focused on improving the physi ian s understanding of the pharmacology and appropriate use f pecific drugs. Such cognitive knowledge will have little t on patient outcomes if the practitioner caring for the atient does not have accurate information on what drugs the tient is *receiving. The added dimension of complete and* ccurate documentation must be considered an integral part *f programs to improve outcomes of our therapeutic efforts.*

Roberta A Monson M D
University of Arkansas for
Medical Sciences
Dept of Medicine
4301 W Markham
Little Rock Ark ~ 05

REFERENCES

1 Monson R A., and Bond C A The accuracy of the medical record as an index of outpatient drug therapy J A.M.A **240** .1‑ 19 ‑
2 Brook R H., Williams K N., and Avery A D Quality assessment today and tomorrow foreca t f r the future Ann Intern. Med **85** 809 1976
3 Sackett D L Haynes R B Gibson E S et al Randomised clini al trial of trategies for improving medi ation compliance in primary hyperten ion Lancet 1 1205 1975
4 Haynes R B Gibson E S Hackett B C et al Improvement of medication compliance in uncontrolled hyperten ion Lancet 1 1 6 19 6
5 Taylor D W Sackett D L Haynes R B et al Compliance with antihyperten ive drug therapy Ann N Y Acad Sci **304** 390 19 8
6 McKenney J M Slining J M., Henderson H R et al The effect of clinical pharmacy on patients with essential hyperten ion Circulation **48** 1104 19 3
7 Freis E D The mismangement of hyperten ion Arch Intern Med **137** 1669 1977
8 Vidt D C The struggle for drug compliance in hyper tension Cardiovasc Clin 9(1) 243 19 8

The Constitution

ne Constitution of the United States is probably the greatest document ever written by man That document could not e been written today!

George E Burch M D
Tulane University School of Medicin
and Charity Hospital of Louisiana
New Orleans La

0002 8703/80/020273 + 01$00 10/0 © 1980 The C V Mosby Co

Letters to the Editor

Failure of prophylaxis for bacterial endocarditis American Heart Association Registry

To the Editor

The American Heart Association (AHA) recognizes that its current recommendations for antibiotic prophylaxis are necessarily empiric This situation has arisen because important clinical information on the efficacy of antibiotic prophylaxis of bacterial endocarditis i lacking The present recommendations are therefore based upon secondary sources of information such as the relative propen ity of various procedures to cause bacteremia in vitro studies of bacteria recovered from the blood the effect of antibiotics on bacteremias the susceptibility of various heart lesions to infection anecdotal ca e reports and the study of experimental models

Although over 30 individual cases of apparent prophylaxis failure have been recorded in the literature many of our colleagues have rightly pointed out that the evidence indicating that a significant number of prophylaxis failures actually occur is inconclusive This question is of con iderable medical and medicolegal importance because of the frequency with which measures to prevent endocarditis are called for and because of the serious con equences of failure to prevent the di ease

In an attempt to accumulate useful epidemiologic data the AHA Committee has established a Regi try to record cases of apparent failure of antibiotic prophylaxis of bacterial endocarditis We are now soliciting case reports Notification may be made on a simple pre printed postcard which will require only identification of the patient and the name address and telephone number of the per on referring the case These po tcard will be made available to physicians and dentists and to any other person or organization requesting them from the AHA or from one of us Alternatively a case may be reported directly to one of us at the address or telephone number li ted below After notification one of us will follow up with a telephone call in order to gather sufficient information to evaluate the case All such information will be confidential

Alth u h there are obviou disadvantages to any retrospective evaluation u h a thi the practical impos ibility of conducting a pro pe ti e trial of different modes of prophylax i has u ed u to seek alternative means of gathering data We h pe that a u ful body of information may be accumu lated whi h ma u the nee future re ommendations for pro

David W Fra er MD
Chief Special Pathogens Bran h
Bacterial Di ea es Divi i n
Bureau of Epidemiol gy
Center for Di ea e Control
Atlanta Ga 3[illegible]3
(404) 329-3[illegible]

Edward L Kaplan MD
Department of Pediatri s
Box 94 Univ rsity of Minne ta
Minneapolis Minn 55[illegible]
(612) 3 3 [illegible]

Mr Mark A O[illegible]
Chief Scientific Council
American Heart As ociation
AHA National Cent r
73[illegible] Greenville Avenue
Dallas Texas [illegible] 31
(214) [illegible]

REFERENCE

1 American Heart Association Committee on Rheumatic Fever and Bacterial Endocarditis Prevention of bacterial endocarditis Circulation 56 139A 1977

Physical training in patients with coronary artery disease

To the Editor

Greenberg and associates dismiss the *marathon r s* immu glaring nity to atherosclerosis *with a sentence* containing exaggerated claim by errors Others have refuted this *as an exa* documenting cases of *fatal* myocardial *infarction* in marathon runners They cite the report from South Afri a which contains detailed clinical data on six marathoners who d el oped apparent heart attacks However only *one* runner died There was no autopsy *however* Scaff reviewed the ECG and found it consistent with *heat stroke* This runner had been taking long training runs *up to 40 miles* in length during the hot urfing season The rema *ning five* runners were alive and running at the time of publication Angiograms were available on four The runner with *the most* severe abnormalities on angiogram *subsequently* completed a 100 mile race Thus the authors did not *refute* the concept of the marathoner s immunity to athero *lerosis* since there is *no evidence of either death or disability* due to this dise se

I have followed 131 cardiac patients *for* 400 patient years after they trained up to marathon distance in *f*ormal rehabil itation program These include 48 with myocardial infarc tion and 19 with coronary bypass Follow up shows that 1[illegible] are alive and running " Of the five who died only one showed progressive atherosclerosis This man ch wed tobacco and swallowed all the juice from three boxes of ch wing t ba co a week I attribute his vascular le ion to the angiotoxic material in tobacco juice and I still consider the marathoner immune to atherosclerosis

Atherosclerosis i the major cau e of death in phy i ians

Greenberg s associates. Therefore I vigorous ly encourage all physicians to conform to a life style which lows them to at least walk the 42 km marathon distance share in this protection[1] Interested physicians are urged to the ranks of the other marathoning professionals in the Medical Joggers Association

Thomas J Bassler M.D Editor
American Medical Joggers Association
Centinela Hospital
P O Box 7?0
Ingleu ood Calif 90307

1 Greenberg M A Arbeit S and Rubin I L. The role of physical training in patients with coronary artery dis ease AM HEART J 97 527 1979
2. Noakes, T., Opie L. Beck W et al. Coronary heart disease in marathon runners Ann N Y Acad Sci 301 593 1977
3 Scaff J H Heart disease in marathon runners N Engl J Med. 295 105 1976
4 Bassler T J Rehabilitation through marathon running West J Med 130 466 1979
5 Bassler T J Physician deaths, J A M A 223 1391 1973
6 Obituaries J A M A 241 625 1979

o the Editor

Bassler[1] has asserted that marathon running (the ability to 42 kilometers) imparts immunity from atherosclerosis The report by Noakes and others[2] contains case reports of infarction in six such marathon runners including one fatal infarction The fatal infarction occurred in a 35 year-old man who for at least one month prior to his death severe exertional chest pain while running. In spite of a s advice and in spite of having to stop running on occasions because of chest pain he continued to run refused medical attention On the day of his death he developed severe chest pain with radiation to the left arm associated with shortness of breath He died shortly after in the Intensive Care Unit An electrocardiogram acute inferior subendocardial ischemia As he had not been running on the day of his death, it is unlikely that either the electrocardiographic changes or the runner s were due to heat stroke It is interesting that all six nners reported by Noakes ignored warning symptoms and running prior to their myocardial infarction

A more recent report by Noakes and co-workers provides autopsy evidence of atherosclerosis in four additional mara thon runners One of these runners died during a 24 km race Another runner with a previous inferior wall infarction and unstable angina died while awaiting bypass surgery This second athlete had angiographically proven progression of his coronary atherosclerosis over a two year period during which he continued marathon running

In evaluating the protective effect of marathon running oronary deaths other factors such as diet smoking habits and self-selection must be considered The incidence of fatal myocardial infarction in young thin non smoking males is extremely low Milvy[4] has estimated that even if marathon running offered no protection at all one would only expect one or at most two fatal myocardial infarctions per year in this group Thus it would be difficult to prove that marathon running conferred immunity from coronary deaths

For the non marathon runner there is even less controversy about coronary deaths Even Bassler[1] reports that fatal myocardial infarctions can occur in non marathon runners. Two of these deaths reported by Bassler occurred in athletes who had won Olympic gold medals and had set world track records

The purpose of our review was to discuss the physiologic effects of exercise in patients with coronary artery disease and its role in treatment Exercise improves cardiovascular fitness and may possibly be beneficial in the prevention of coronary heart disease Claims of total immunity from atherosclerosis in a highly selected group do not substitute for careful epidemiologic studies. Furthermore these claims may dis suade athletes and joggers from responding appropriately to warning symptoms of impending coronary events

Mark A Greenberg M.D
Director Coronary Care Unit
Ira Rubin M.D
Director Electrocardiography Dept
Montefiore Hospital & Medical Center
111 E 210th St
Bronx N Y 10467

REFERENCES

1 Bassler T J Marathon running and immunity to atherosclerosis Ann N Y Acad Sci. 301 579 1977
2 Noakes T D Opie L. H., Beck, W McKechnie J., Benchimol, A., and Desser K Coronary heart disease in marathon runners Ann N Y Acad Sci. 301 593 1977
3 Noakes, T Opie L. Rose A G and Kleynhans, P H T Autopsy proved coronary atherosclerosis in marathon runners N Engl J Med 301 86 1979
4 Milvy P Statistical analysis of deaths from coronary heart disease anticipated in a cohort of marathon run ners Ann N Y Acad Sci 301 620 1977

Asystole after pacemaker placement

To the Editor

A recent Letter to the Editor (AM HEART J 97 815 1979) described carotid sinus hypersensitivity resulting in cardiac asystole and hypotension The asystole was treated by cardiac pacemaker but significant hypotension and resulting symptoms persisted We recently reported a similar case in which the symptoms and hypotension which persisted after successful cardiac pacemaker placement were relieved by bilateral surgical denervation of the carotic sinuses

Lyle Steiner M.D
Lewis Sasse M.D F.A.C.C
Southern California Permanente
Medical Group
1505 N Edgemont St
Los Angeles Calif 90027

REFERENCE

1 Sassé L. Permanent demand pacemaking (Letter to Editor) J Thorac Cardiovasc Surg 67 671 1974

Book reviews

Clinical Phonocardiography and External Pulse Recording By Morton E Tavel M D Chicago and London 1978 Year Book Medical Publishers Inc 391 pages

This is a good book which has been well received The pulse recordings and phonocardiograms are thought provoking They stimulate interest and understanding of the mechani al and physiologic events of the cardiac cycle The discussions are interesting some of which this reviewer either does not understand or accept For example the author on pages 122 and 123 states that when the third and fourth heart sounds constitute a single ound this is termed a summation gallop This reviewer has always thought that the cadence of a galloping horse constituted a gallop rhythm of the heart sounds and not merely a single sound This needs clarification The cadence of a gallop rhythm is heard on auscultation and is difficult to appreciate readily from a recording Regardless of such details in clinical cardiology the recordings are good and the mechanical and hemodynamic significance of the components of the various tracings are of extreme value to undergraduate students housestaff and physicians who are in training in cardiology This is a book that requires critical and thoughtful reading This is a good book—a book worth own ing

The Clinical Recognition of Congenital Heart Disease By Joseph K Perloff M D Philadelphia 1978 W B Saunders Company 781 pages Price $43 50

This second edition of Perloff's monograph written in textbook format on congenital heart disease is an excellent review of the subject The text is written for clinicians with special procedures such as cardiac catheterization included for those who engage in this procedure as well as for clinicians who must depend on the data obtained by the various special procedures. It is impossible to review this entire book criti cally However it is interesting to find a chapter on primary pulmonary hypertension in a book on congenital heart disease Surely this is an important disease in all age groups but is it congenital? This book is a very good ingle source of information for clinicians on congenital heart disease It is a book worth owning for study and for reference

Understanding Cardiology By Hywel Davies M.A DM F.R C P., and William P Nelson M D Boston and London, 1978 Butterworth & Co Ltd 424 pages Price $?9 95

This is a practice book on clinical cardiology The authors have introduced recordings of hemodynamic phenomena into bedside clinical cardiology They fail however to emphasize adequately the limited need for hemodynamic phonocardiographic or other recordings in the daily practice of cardiology or general medicine There is a need to learn when special procedures are necessary for the actual care of patients The illustrations are numerous and excellent The diseases discussed are fairly complete and the presentations are lucid and brief The authors have summarized for the beginner pertinent information This book is intended for beginners in medicine and cardiology but must be supplemented by much more extensive reading and study The bibliographies are good but far from adequate This is a good book for clinicians, especially undergraduate students housestaff and family physicians The chapters on electrocardiography arrhyth mias and echocardiography are particularly inadequate and would require more extensive study The presentations of these important aspects of cardiology are somewhat superfi cial Readers will need to supplement these subjects in greater detail This is a very brief summary of a large subject clinical cardiology

Heart Disease in Infancy and Childhood By John D Keith, Richard D Rowe and Peter Vlad New York 19 8 Macmil lan Publishing Company Inc 1083 pa es Price $50 00

This is an outstanding book on heart disease in infants and children The first two editions were a great success and were used worldwide The third edition brings the subject up to date For example the use of echocardiography and His bundle recordings are now thoroughly discussed The contrib utors are numerous and the respective contributions are nicely integrated with that of the others This book is complete enough to provide a thorough knowledge of clinical cardiology in infants and children This is an excellent book which should be in the library of all pediatricians and all cardiologists, including adult cardiologists

Books received

Rehabilitat on After Myocardial Infarct on Unit 2 By Rebec ca M. Garcia R N M S N New York 19 + Appleton Century-Crofts, Inc 3 pages Price $ ..

Arterial Hypertension Report of WHO Expe Committee Geneva 1978 World Health Organization 8 pages

Drugs Lipid Metabolism and Atheroscleros s Edited by David Kritchevsky Rodolfo Fa letti and Willi m L H lmes New York 1978 Plenum Publ shing C rp 4? p es Price $?? ,0

Trauma to the Heart and Great Vessels By Panagiotis N Symbas M D., New York 1978 Grune & Stratton Inc 200 pages Price $22.50

Cardiovascular Med cine Controversies Edited by Clive Wood New York, 1978 Grune & Stratton Inc 83 pages Price $10.25

Atti VIII Congresso Nazionale Catania 1 3 Aprile 1977 Edited with the collaboration of Crippa F Berger Rome 1977 Luigi Pozzi Publisher 859 pages.

Cardiac and Pulmonary Imaging

The Department of Radiology and the Office of Continuing Education of the University of California San Diego School of Medicine are offering a course entitled "Cardiac and Pulmonary Imaging," to be held on February 8 through 10 1980 in San Diego The Program Director is Michael J Kelley M D and the guest faculty includes Arthur D Hagen M D., Walter L. Henry M D Martin J Lipton M D Charles L. Putman M D and Lewis Wexler M D Participating faculty of the University of California will include Naomi P Alazraki M D William L. Ashburn M D., Joseph J Bookstein M D Marc N Coel, M D., David S Feigin M D John W Forrest M D Paul J Friedman M D Victor F Froelicher M D Charles B Higgins M D Michael J Kelley M D., Kenneth M Moser M D Ralph Shabetai M D., and Andrew T Taylor Jr M D Fee for the course is $?25 00 and 19 hours of Category I AMA credit will be given For further information contact Mary J Ryals Radiology P O Box ?305 La Jolla Calif 9?038 Telephone (714) 459 9 8?

Dr Heinz Karger Prize 1979

The Dr Heinz Karger Prize awarded every year in memory of the well known Basel publisher for an outstanding scientific work has been awarded in 1979 to Dr Louis Tobian U S A for his paper "Evidence for Na retaining humoral agents and vasoconstrictor humoral agents in hypertension prone Dahl S rats Prevention of NaCl induced hypertension in Dahl S" rats with thiazide "

For 1980 the Dr Heinz Karger Memorial Foundation invites the submission of papers on the topic Antibodies with intrinsic biological activity " The paper must be an original research work and must reach the publisher no later than February 28 1980

For 1981 the Foundation invites the submission of original research papers on the subject Intestinal absorption of peptides." Papers must reach the publisher no later than February 28 1981

Manuscripts shall not exceed 20 typewritten pages including illustrations tables and bibliography Manuscripts must be typewritten on one side only double-spaced submitted in quadruplicate and must be marked Competition in accordance with the instructions contained in Rules for the Preparation of Manuscripts This leaflet can be obtained free of charge from the publishers Papers may be written in English French, or German Papers should be mailed well within the deadline date to S Karger AG Arnold Bocklin Strasse 25 CH-4011 BASEL Switzerland

The winning paper for each year will be published in English in one of the Karger journals The award will be 7 000 Swiss francs The Council of the Foundation will judge the papers and will confer the prizes

Seminar on Cardiovascular Epidemiology and Prevention

The Council on Epidemiology and Prevention of the International Society and Federation of Cardiology announces its thirteenth Ten Day International Teaching Seminar on Cardiovascular Epidemiology and Prevention to be held near Kaunas Lithuanian S S R., U S S R on August 16 through 29 1980 Approximately 30 Fellows will be selected Nominees should normally be at the postgraduate level with some residency training or its equivalent and be interested in cardiovascular disease epidemiology Partial assistance with travel costs may be available for accepted Fellows. Room and board are provided without cost Fluency in English is an absolute essential Applications including (1) a letter of nomination by the chief of the nominee s department or institution (2) a personal letter of application from the nominee and (3) the applicant s curriculum vitae should be received before March 15 1980 by Rose Stamler Seminar Coordinator 303 E Chicago Ave Room 1-615 Chicago Ill. 60611

University of Arizona Travel Study Program

Two separate sessions of a seminar entitled Recognition and Management of the Stroke Prone Patient" will be offered this spring The first will be held on March 15 through 22 at The Mark Resort Vail Colorado The second session will take place on May 3 through 9 at Frenchman s Reef St Thomas, U.S Virgin Islands. Each session will carry 25 hours of approved Category I AMA credit For registration materials and further information contact Office of Continuing Medical Education Attn Faith Carlisi, University of Arizona Health Sciences Center Tucson Ariz 85724 Telephone (602) 626-6173

Atherosclerosis in nonhuman primates

In conjunction with the VIIIth Congress of the International Primatological Society scheduled for July 7 through 12 1980 in Florence Italy a symposium entitled "Regression of Atherosclerosis in Nonhuman Primates to be held on July 5 is being organized Persons who wish to present 10-minute research papers related to the symposium topic are invited to submit four copies of a 300 word abstract to M R Malinow M D Oregon Regional Primate Research Center 505 N W 185th Ave Beaverton Oregon 97006 U.S.A Abstracts must be postmarked no later than February 28 1980 and must include title page with the author s name title position and mailing address

Nuclear Medicine Course

The Department of Radiology and the Office of Continuing Education of the University of California San Diego School of Medicine are offering a course entitled Cardiovascular Nuclear Imaging to be held on February 6 and 7 1980 in San Diego The Program Director is William L. Ashburn M D., and the guest faculty includes David L. Gilday M D., and Glen W Hamilton M D Participating faculty of the University of California will include Naomi P Alazraki, M D., William L. Ashburn, M D Victor F Froelicher M D Samuel E Halpern M D., Kenneth M. Moser M D Robert A Slutsky M D., Andrew T Taylor Jr., M D and John W

Verba Ph.D Fee for the course is $200 and 11½ hours of Category I CME credit will be given For further information, contact Mary J Ryals Radiology P O Box 2305 La Jolla Calif 92038 Telephone (714) 459 9787

HLA System and Clinical Medicine

A symposium entitled "The Relevance of the HLA System and Clinical Medicine" will be presented at the Hilton Hotel San Diego California on March 15 and 16 1980 The symposium is designed to update current information related to the HLA system and aspects of clinical medicine A significant association has been demonstrated between HLA antigens and various diseases. The symposium will emphasize the importance of HLA testing in transplantation, paternity testing, and diagnosing various diseases. Fourteen hours of AMA CMA credit will be available For further information contact Edith Bookstein Program Assistant University of California at San Diego Office of Continuing Education M-017 La Jolla Calif 92093 Telephone (714) 45[illegible]-3[illegible]04

American Heart Journal

March 1980 Volume 99 Number 3

Editorial

From heart to brain the new definitions of death

Peter McL Black M D Ph D
Boston Mass

In our society, physicians are generally responsible for declaring a person dead they usually require cessation of cardiorespiratory activity to make this declaration Recent social and medical developments however have significantly changed both the concept of death and the criteria for its pronouncement Instead of considering the heart as central to the determination of death some physicians are now using death of the brain as adequate for death despite continued cardiac function

It does seem that death of the brain is an important item even in traditional cardiac declarations of death If someone s heart dies but his brain can be kept alive by an artificial heart or by a transplanted one he is not considered dead just because his own heart no longer functions If his heart stops every attempt is made at resuscitation because of the possibility that his brain might be kept perfused while his cardiac arrest is rectified Now that physicians can keep the heart and lungs working even with a brain that has been destroyed it is predictable that explicit attention be paid to death of the brain as an adequate criterion for death in general

The concept that death is in fact brain death is being increasingly accepted in the United States This is reflected in our courts and our lawmaking bodies as well as in medical practice The National Conference of Commissioners on Uniform State Laws for example has recently approved the Uniform Brain Death Act This proposal states

For medical and legal purposes, an individual with irreversible cessation of functioning of the brain including the brain stem is dead Determinations of death under this act shall be made in accordance with reasonable medical standards

This is a proposal to be placed before state legislatures to achieve a uniform standard for the declaration of death At least 18 states have already passed some kind of brain death legislation and several courtroom decisions have also made it clear that brain death is considered an adequate criterion for death in many jurisdictions

In most cases the physician has to deal with this changing definition of death makes little difference The prolonged absence of respiration and circulation that allows a diagnosis of death in most cases today is presumptive evidence of brain death as well since the heart is more resistant to anoxia and failed circulation than is the brain However there are some cases in which the brain will have suffered widespread irreversible damage although the heart still beats It is th tua tions that brain death criteria were for[1] It should be noted that none of intended to cover emergency situations by none of them can one declar ent s dead durin attem ts at cardi suscit

From the Neur su gic l Servi e Massachusetts General Ho pital Boston Mass

Rece ed for publicati n Mar 6 19 9

Reprint requests Pet r McL Black Mass chusett General Hospital Boston Mass 0?114

000?-8 03/80/030?/9 + 03$00 30/0 © 1980 The C V Mosby Co

They are all formulated to deal with some period of continued cardiac activity without apparent brain activity in a patient requiring respiratory support

Criteria for brain death

Several approaches have been advocated to establishing brain death criteria They have as a common goal the diagnosis of irreversible widespread brain destruction Such destruction may be demonstrated pathologically or may be implied from a failure of bodily survival despite all treatment after criteria have been fulfilled Some criteria require only physical examination in the appropriate setting others require one or more isoelectric electroencephalograms (EEGs) as well still others recommend a demonstration that all cerebral circulation has ceased [4]

Certain physical findings are a part of all criteria These include absence of brain stem reflexes spontaneous respiration and co-ordinated movement in the appropriate setting Other items may vary there may be reflex withdrawal of an arm or leg, which indicates only spinal cord activity Pupils need not be widely dilated but must be fixed to light The time interval required to establish these findings may vary

In 1976 a conference of the Royal Colleges and Medical Faculties of Great Britain stated that physical examination in the correct setting was enough to establish brain death These criteria require certain preconditions to be fulfilled and appropriate examinations to be completed The preconditions are the exclusion of drug overdosage, hypothermia, or metabolic disturbance as possible causes and the requirement that the patient be maintained by a respirator The appropriate examination is that of brain stem function pupils should be fixed to bright light there should be no gag reflex or facial movements and there should be no breathing despite a pCO_2 above the level required for respiratory stimulation These criteria explicitly include any requirement for an EEG establish that a neurologist is only necessary if the diagnosis [illegible] and leave the time interval variable depending on the cause of brain death.

The so-called H[illegible] are criteria based on physical ex[illegible] well They make provision for an [illegible] EEG as being "of great conf[illegible] but the major requirements are [illegible] unction including absence of respiratory effort They differ from the British criteria in requiring a 24 hour period in which there can be no change in the findings

The committee of the American Neurological Association to study brain death has incorporated a blood flow technique into their recommendations. They suggest that one of two methods can be used to make the diagnosis One method is to demonstrate intracranial circulatory arrest for 30 minutes. This approach widely used in Europe has also recently been proposed by a collaborative study group here Theoretically the brain cannot survive 30 minutes without blood flow Practically several studies have demonstrated that widespread destruction follows such an interval [4] The demonstration of failure of circulation to the brain may therefore be an important method of establishing brain death Normally this demonstration has been done by angiography requiring transfemoral catheterization in an angiogram suite New radioisotope techniques however, may make it possible to use this criterion more conveniently in any hospital with a nuclear medicine department

In the situation where an attempt is not made to show intracranial circulatory arrest there is a more complicated procedure proposed by the committee of the American Neurological Association For this option several items are necessary There can be no pupil response to bright light, no movement of the eyes when twenty c.c. of ice water is instilled into either ear, no gag or corneal reflex or any other cranial nerve reflex, and no decerebrate or decorticate posturing One EEG showing electrocerebral silence is "strongly recommended" There must be no spontaneous respiration Perhaps most important the patient must be observed for long enough (minimally 12 hours, perhaps as long as 72 hours) to assure that drug intoxication metabolic and other reversible abnormalities are not responsible for the neurological findings

These criteria are the most recent attempt to develop broadly acceptable guidelines for brain death within the United States They have been approved by the major neurological and neurosurgical organizations in the country while presenting explicit tests they also allow for variation depending on the circumstances The variable time interval the option of a single blood flow determination and the recommended but not

required EEG represent flexibility while still assuring that no recovery will be possible

Goals of brain death criteria

The present diversity of criteria in brain death may be disconcerting to some physicians. It is in part a result of historical development which has occurred on two levels. The first is the philosophical and social—the acceptance of the idea that death of the brain is death of the person. This concept must be acceptable to a wide spectrum of society to provide impetus for work on the second level. It has however been increasingly accepted in the United States as the Uniform Brain Death Act exemplifies.

The second level is deciding what will be adequate evidence of a dead brain. This is a medical concern primarily and legislators and judges have left it for physicians to decide. However it is not an easy matter. The criteria adopted may reflect the goals of the adopters.

Consider for example the British criteria. These appear to have been developed primarily to achieve agreement for practical purposes throughout Britain. The work of the courts, of transplant teams and of practicing physicians was made more difficult by uncertainty in this area. A uniform simple set of rules was therefore drafted which required nothing more than physical examination.

This approach may not allow for technological progress in such areas as blood flow determination. It has an arbitrary quality that may be distasteful to some. Perhaps most important it has been very difficult to achieve similar consensus in the United States.

There are therefore other goals than pragmatic agreement that brain death criteria might aim for. They might for example try to predict the pathological findings of a dead brain at postmortem. However this goal has also been difficult to achieve; there is significant disagreement about how much brain destruction is enough to qualify as a dead brain and the differences between changes occurring before and after cardiac arrest have not always been easy to define.

Many physicians have therefore used a third approach to guide the development of brain death criteria. This is the goal of predicting no survivors once criteria have been met. This has been done best for the Harvard criteria. From published data a few weeks at most is the maximum time that cardiac function continues.[1] The reason for this is still unclear; presumably it indicates a relationship between cardiovascular control and the brain stem that has not yet been clarified. By whatever mechanism however it appears that irreversible hypotension and cardiac arrest follow inevitably upon the fulfillment of the Harvard criteria.

For other proposed criteria the situation has not been quite as well established. The criteria of the collaborative study group which resemble those of the American Neurological Association guaranteed cardiac arrest within 12 weeks of brain death. These criteria are considerably broader in scope than the Harvard criteria yet still seem reliable in guaranteeing failure of survival.

It does appear that no one who fits present criteria for brain death will survive it all despite everything that can be done, let alone some day recover neurological function. Brain death is quite different from a state of perpetual coma primarily in failure of respiratory drive and absence of all brain stem function. It is a state approaching cardiac death so closely that it seems reasonable to redefine death to include it.

It is an important task however to develop criteria for its determination that will be acceptable throughout the United States while allowing for change with advancing knowledge. The criteria proposed by the American Neurological Association appear to be the most significant recent contribution to this task. If continued testing demonstrates that they preclude survival despite all therapy these criteria may become the standard for brain death within the United States.

REFERENCES

1. Internal Medicine News 11(20) 1 Oct 15 19 8
2. Veith F J Fein J M Tendler M M et al. Brain death J A M A 238 1651 1744 1977
3. A definition of irreversible coma: report of the Ad Hoc Committee of the Harvard Medical School to examine the definition of brain death, J A M A 205 337 1968
4. Black P McL. Brain death, N Engl J Med. 299 338 393 1978
5. Conference of Royal Colleges and Faculties of the United Kingdom: diagnosis of brain death. Lancet 2 1069 1976
6. Report of the Committee on Irreversible Coma and Brain Death in Trans. Am Neurol. Assoc 102 192 1977
7. An appraisal of the criteria of cerebral death: a summary statement: a collaborative study. J A M A 237 982 19 6
8. Goodman J M and Heek, L. L. Confirmation of brain death at bedside by isotope angiography. J A M A 238 966 1977

The effects of atropine administered with standard syringe and a self-injector device

Thomas R Martin, M D
John A Kastor M D
Kenneth L Kershbaum M D
Karl Engelman M D
Philadelphia, Pa

Whether or not to employ atropine during the course of myocardial infarction has become a matter of some controversy in recent years[1-15] The value of the drug is based on the presumption that bradycardia may induce ventricular arrhythmias and decrease cardiac output during acute myocardial infarction *Judicious* increase in heart rate it is thought might prevent potentially fatal ventricular fibrillation from developing and increase perfusion of vital organs in particular the myocardium

Opposition to the use of atropine in myocardial infarction has been supported by findings in dogs with experimentally created ischemia that increases in heart rate lower the fibrillation threshold and enhance the tendency for dangerous ventricular arrhythmias to arise[3-9] Furthermore vagotonia appears to have a protective effect in some experimental models Examples in man of increased ventricular irritability ischemia and hypotension arising after the administration of atropine during myocardial infarction have also tempered the unqualified enthusiasm for the use of this drug during an acute coronary event

The need for the drug in particular cases however is not disputed The hypotensive patient with sinus bradycardia a junctional rhythm and/or A V nodal block induced by vagotonia certainly appears to benefit by an appropriate increase in heart rate At this writing there is no widely accepted consensus about how often and how generally atropine should be administered during an acute myocardial infarction

Administration of the drug by intravenous injection is the favored technique in order to produce rapid onset of action and assure absorption However this method is not always appropriate An intravenous line may not be in place or proper infusion equipment may not be available outside the hospital Intravenous administration of the drug can be difficult for untrained personnel and even for skilled workers in the acute situation where vasoconstriction is present In these particular instances where atropine may be needed and the intravenous administration cannot be carried out a self injection device with relatively rapid onset of drug effect could be useful One such device is the Atropen which delivers 2 mg of atropine in a citrate buffer intramuscularly In this report we present the results of a study conducted in healthy volunteers to evaluate the effectiveness of this device in accelerating heart rate and to compare its properties with those of more accepted methods of administering atropine

Methods

Atropen is a spring loaded cylindrical device* which contains 1 67 mg atropine base (equivalent to 2 0 mg atropine sulfate) in 0 7 ml of citrate

From the Cardiovascular Section Department of Medicine of the University of Pennsylvania School of Medicine and the Hospital of the University of Pennsylvania Philadelphia Pa

Supported in part by a contract (NIH NHLBI [illegible]) with the United States Public Health Service

Received for publication Dec [illegible] 1978

Accepted for publication May 1 1979

Reprint requests Dr John A Kastor Chief Cardiovascular Section [illegible] Hospital of the University of Pennsylvania Philadelphia PA [illegible]

*Developed by Survival Technology Inc Bethesda Md

0002-8703/80/030282 + 0 $00 70/0

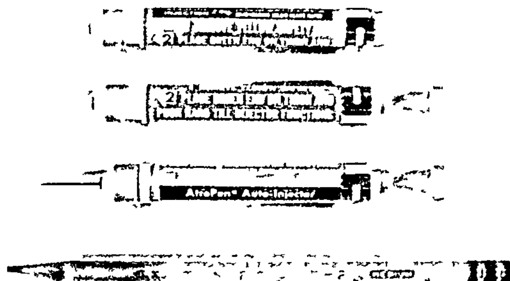


Fig 1 The Atropen device is illustrated as provided *(top example)* after removal of the safety cap *(second example)* and after extension of the needle *(third example)*

Table 1 Significance among different methods of administering atropine

	Resting rate	Peak rate	Time to 5" rate increase	Time to peak rate	Duration of rate increase
IV versus sulfate IM	NS	NS	< .001	< .001	< .001
IV versus citrate IM	NS	NS	< .001	< .001	< .05
IV versus Atropen	NS	NS	< .001	< .001	< .025
Sulfate IM versus citrate IM	NS	NS	< .005	< .05	NS
Sulfate IM versus Atropen	NS	NS	< .001	< .001	NS
Citrate IM versus Atropen	NS	NS	< .001	< .01	NS

buffer solution (pH 4 3) (Fig 1) When the safety cap is removed and the instrument is pressed against a muscle mass preferably the quadriceps femoris of the thigh the spring mechanism is automatically released rapidly extending the needle to a tissue depth of ⅞ inch within 4 msec Injection of the contents of the Atropen is completed in 260 msec (Data on file with Survival Technology Inc Bethesda Md) Atropine base in citrate buffer is used in preference to atropine sulfate because of its greater stability when stored in the Atropen device

Fifteen healthy volunteers ranging in age from 21 to 35 years served as subjects None had a history of cardiovascular or autonomic nervous system disease urinary retention or glaucoma There were 12 women and three men Their average weight was 130 pounds with a range of 108 to 170 pounds None had taken drugs coffee tea or sodas or had smoked cigarettes in the 12 hour period before each study trial Informed consent was obtained from each subject

Each volunteer received four injections administered in a randomized sequence with one injection on each of four successive days Injection conditions were defined as follows (a) 1 0 ml solution containing 1 0 mg atropine sulfate (0 835 mg atropine base) injected intravenously with a conventional syringe (b) 2 0 ml solution containing 2 0 mg atropine sulfate (1 67 atropine base) injected intramuscularly with a conventional syringe (c) 2 0 ml solution containing 1

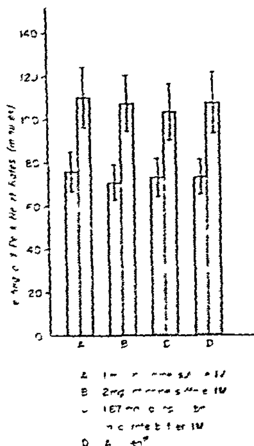


Fig 2. Graphic representation of the effects of atropine on heart rate

atropine base in a citrate buffer solution (as contained in Atropen) injected intramuscularly with a conventional syringe (d) Atropen injection containing 1.67 mg atropine base in a citrate buffer solution. Intravenous injections were made into an antecubital vein and intramuscular injections were made into the anterior surface of the thigh. The intramuscular dosage was selected as twice the intravenous dose most often used in coronary care units on the assumption that the total effects on heart rate would be similar.

All subjects were studied in the supine position in a quiet room. Following a 20-minute rest period before each injection trial blood pressure (arm cuff) and radial pulse rates were recorded at two-minute intervals until both were stable for at least ten minutes. The injection was then completed and continuous electrocardiographic records were made during the first ten minutes of each trial to permit precise measurement of changes in heart rate during this period. Pulse rate was measured every minute for ... minute every three minutes for the next ... then every two minutes for the next ... utes. Peripheral blood pressure was measured every ten minutes throughout the trial.

When the rhythm was stable the heart rate was determined at 15-second intervals from the electrocardiographic strips by measurement of three consecutive R R intervals. In the presence of sinus arrhythmia the rate was computed as an average from three randomly selected groups of three R R intervals.

After the completion of each injection, the responses for heart rate versus time and blood pressure were determined for each trial in every patient. The following characteristics of the heart rate response produced by each injection modality were studied: (1) resting heart rate (2) peak heart rate (3) time to onset of cardioacceleration (defined as a heart rate increase of greater than or equal to 5% above the resting heart rate) (4) time to peak heart rate (5) duration of heart rate increase above resting heart rate.

Subjects were questioned about side effects experienced during each study period. Many of the subjects were nurses and consequently were familiar with some of the side effects of atropine before the study began.

Statistical significance of the results was tested by Student's t test and all data were expressed as mean ± one standard deviation.

Results

Changes in heart rate The heart rates for each of the subjects increased significantly when atropine was administered regardless of the technique employed (Fig 2, Table I). The cardioacceleration developed from mean control rates, which were similar and not significantly different among the four modalities of administration to peak rates which were also similar and not significantly different among the four modalities: 1 mg atropine sulfate intravenously—values from 76 ± 9 beats/minute control to 110 ± 14 beats/minute after the drug; 2 mg atropine sulfate intramuscularly—values from 71 ± 8 beats/minute control to 107 ± 13 beats/minute after the drug; 1.67 mg atropine base in citrate buffer intramuscularly—values from 73 ± 9 beats/minute control to 103 ± 13 beats/minute after the drug; Atropen—values from 73 ± 8 beats/minute control to 107 ± 4 beats/minute after the drug.

Intravenously administered atropine sulfate produced the most rapid onset of action (recognized by ≥ 5% increase in heart rate) 0.8 ± 0.4

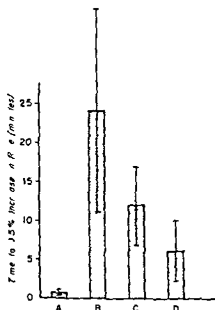


Fig 3 Graphic representation of the speed by which atropine increased heart rate For A B C D code see *Fig* 2

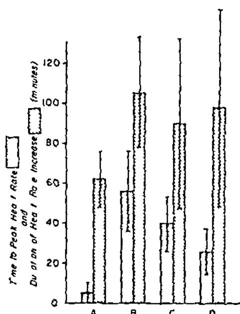


Fig 4 Graphic representation of the time to peak heart rate and duration of heart rate increase produced by atropine For A B C D code see *Fig* 2

minute and this time was significantly shorter than for each of the other three modalities (Fig 3 Table I) Atropen produced significantly quicker onset of cardioacceleration 6 ± 4 minute than did intramuscular atropine sulfate 24 ± 13 p < 001 or intramuscular atropine in citrate buffer 12 ± 5 minute p < 001

The *time to peak heart rate* was significantly different among each of the four modalities when compared with each of the others (Fig 4 Table I) The intravenous method produced the most rapid increase to peak heart rate 5 ± 5 minute Atropen was second most rapid at 26 + 13 minute atropine in citrate buffer intramuscularly followed at 40 + 15 minute and atropine sulfate intramuscularly produced the slowest response 56 ± 20 minutes

The *duration of heart rate increase* was significantly shorter when produced by intravenous administration and compared with each of the intramuscular methods (Fig 4 Table I) intravenous atropine 62 ± 34 minute intramuscular atropine sulfate 105 ± 27 minute intramuscular atropine in citrate base 90 ± 12 minute Atropen 98 ± 18 minute Among the three intramuscular techniques the differences for duration of heart rate increase were not significant

Cardiodeceleration Initial transient cardiac slowing was detected in only three subjects after intravenous atropine whereas transient slowing was noted in ten subjects after Atropen and in nine after intramuscular atropine citrate and atropine sulfate Slowing of the heart rate did not occur after any injection in four of the 15 subjects The occurrence of sinus nodal slowing did not correlate with weight or the mean resting heart rate of the subjects

Blood pressure Both systolic and diastolic blood pressures rose following atropine but the extent of the responses did not differ significantly among the trials

Side effects There was no significant difference in the frequency of dry mouth Blurred vision was somewhat more frequent after Atropen (13 subjects) than after intravenous (seven subjects) or intramuscular (nine subjects) atropine sulfate Pain at the intramuscular injection site did not trouble the subjects after any of the injections and Atropen did not cause increased discomfort during injection

Discussion

Atropine induced cardioacceleration The most striking differences among the various methods employed in this study to administer *intramuscular* atropine relate to the time course of the increase in heart rate We found that Atropen produced a significantly earlier effect compared with conventional administration of either atropine sulfate or atropine citrate



Fig 5 Radiograph showing the dispersion of radiopaque material in an anesthetized 175 pound Newfoundland dog The discrete globules on the right are the result of five injections with a conventional syringe The more widely dispersed patches resulted from injections with Atropen

Both mechanical and biochemical factors appear to contribute to the faster action of Atropen It is a spring loaded device whose contents are injected more rapidly and under greater pressure than can be achieved with a conventional syringe This results in a wider tissue dispersion immediately after injection (Fig 5)

The biochemical basis for the observation that atropine in citrate buffer (pH 4 3) acts more rapidly than unbuffered atropine sulfate is not known The extent of dissociation of the two compounds immediately after injection may be a factor Buffered atropine citrate complex may be more stable after injection than atropine sulfate and dissociate to a lesser extent The undissociated form of a salt is uncharged and uncharged molecules penetrate capillary lipid membranes more rapidly than do charged molecules Consequently the atropine citrate complex would be expected to enter the bloodstream faster than the more dissociated charged atropine base in atropine sulfate

Atropine induced cardiodeceleration Sinus nodal slowing is a manifestation of the transient paradoxical parasympathomimetic effect which occurs soon after parenteral administration of atropine In our study cardiac slowing occurred in some patients after administration of atropine intramuscularly regardless of the type of solution or method of injection Kalser and McLain[31] have established that slowing of heart rate after parenteral atropine occurs only when plasma concentration of atropine is low, the heart rate then increases as serum concentration of the drug rises[31] This supports experimental observations that slowing occurs after small intravenous doses of atropine (0 3 to 0 6 mg intravenously) after larger intravenous doses administered slowly, and after intramuscular injections (because of slow absorption into the bloodstream) but less frequently after rapid intravenous injection of larger doses The rarity of sinus slowing after intravenous atropine noted in our study may be related to the relatively large size of the dose (1 0 mg) or to the rapid rate of intravenous administration of the drug

While the parasympathomimetic property of atropine has been well documented its mechanism and significance remain unclear This effect is widely attributed to a central mechanism from observations that cardiac slowing could be abolished by general anesthesia as well as by sectioning the vagus nerve and that cardiac slowing could be produced in turtles by direct perfusion of the brainstem with atropine More recently however the central origin of this effect has been

questioned by demonstrations that homatropine methylbromide a quaternary ammonium compound that does not penetrate the blood brain barrier will also cause transient cardiac slowing[3]

Blood pressure In supine normal subjects atropine may elevate systolic and diastolic pressures[3] The rise in both pressures reported here is probably caused by peripheral vasoconstriction rather than by an increase in cardiac output which would produce a decrease in diastolic pressure and elevation of pulse pressure

Cardiac toxicity All subjects in this study maintained sinus rhythm following atropine administration However attention has been called to the occurrence of transient arrhythmias including AV dissociation after intravenous administration of atropine to subjects without myocardial arrhythmias[37 38] In one such study a relatively large intramuscular dose of 11 0 to 14 0 mg of atropine sulfate was necessary to produce AV dissociation in healthy volunteers[38] Reports have also appeared describing increased ventricular irritability following intravenous injection of atropine in such subjects[3 39] In each of these cases the ventricular beats occurred during the period of tachycardia produced by the drug To our knowledge no reports of ventricular irritability during the transient period of cardiac slowing have been published

Use of atropine during myocardial ischemia or infarction The administration of atropine in a self injection device reliably produces cardioacceleration in normal subjects The effect is more rapid than with conventional intramuscular methods but slower than by intravenous infusion The amount of heart rate increase is similar regardless of the method used in the dosage established in this study But normal subjects are obviously different from patients with acute myocardial infarction What will be the effect of such a drug in these patients?

Stuckey and associates[9] have evaluated 27 patients in a coronary unit 17 of whom had definite myocardial infarction In these patients Atropen raised the heart rate from an average rate of 51 beats/minute to 96 beats/minute in 30 minutes Significant bradycardia was not produced by the injection Increase in systolic pressure followed use of the drug In two cases increased chest pain developed In this group of patients Atropen was effective in producing cardioacceleration

It seems highly unlikely however that a study comparable to the one reported here could be conducted in acutely ill patients with coronary disease in order to establish the relative effects of atropine given by different methods Valuable as such data may be we will have to depend on information which can be obtained in the controlled setting of a group of healthy subjects It seems probable though not established that similar results would appear

Although Atropen has been established as an effective and we suggest more effective method of delivering atropine where intramuscular or self injection is needed the fundamental question about the clinical application of the drug remains unanswered Such a discussion is beyond the intent or scope of this study Our support for the use of the drug in a self injection device is based upon the following (1) the method is effective in relieving vagal tone and elevating heart rate (2) Atropen produces a more rapid response than do conventional intramuscular injection methods (3) some patients with acute myocardial infarction bradycardia and hypoperfusion benefit from administration of atropine (4) some of these patients may be successfully treated outside the hospital when a self injection device may be particularly useful

The authors would like to thank the following physicians and nurses who assisted in the study Gary Gerstenblith M D Mark Poster M D Catherine Haines R N Charlotte Mohuddin R N Karen Shibley R N Carolyn Williams R N We are also indebted to Mr Chuan Shue Lee for statistical support Ms Eileen Golden and Ms Muriel Morris for secretarial assistance and to Drs George C Koelle Joseph K Perloff and Alfred P Fishman for valuable advice

REFERENCES

1 Haden R F Langsjoen P H Rapoport M J and McNerney J J The significance of sinus bradycardia in acute myocardial infarction Dis Chest 44 168 1963
2 Lown B Vassaux C Hood, W B Jr Fakhro A M Kaplinsky F and Roberge G Unresolved problems in coronary care Am J Cardiol 20 494 1967
3 Adgey A A J, Geddes J S Mulholland H C, Keegan D A J and Pantridge J F Incidence significance and management of early bradyarrhythmia complicating acute myocardial infarction Lancet 2 1097 1968
4 Gregory J J and Grace W J The management of sinus bradycardia nodal rhythm and heart block for the prevention of cardiac arrest in acute myocardial infarction Progr Cardiovasc Dis 10 505 1968
5 Pantridge J F, and Adgey A A J Pre hospital coronary care the mobile coronary care unit Am J Cardiol 24 666 1969
6 Han J Mechanisms of ventricular arrhythmias associated with myocardial infarction Am J Cardiol 24 800 1969
7 James T N Pathogenesis of arrhythmias myocardial infarction Am J Cardiol 24

Levine H J Pre-ho pital management of acute myocardial infarction, Am. J Cardiol 24 826 1969
Lown B., Klein M D., and Hershberg P I Coronary and precoronary care Am J Med. 46 705 1969
Lyon L J Donoso E and Friedberg C K Temporary control of ventricular arrhythmias by drug induced sinus tachycardia Arch. Intern Med 123 436 1969
Adgey A A J., Allen J D Geddes J S., James R G G Webb S W Zaidi, S A. and Pantridge J F Acute phase of myocardial infarction Lancet—September 4 1971 pp 501 504
Editorial Atropine after myocardial infarction Lancet—Dec 2, 1972, pp 1183-1184
Epstein S E Redwood D R and Smith E R Atropine and acute myocardial infarction, Circulation 45 1273 197_
Sarnoff S J Heart rate in acute myocardial infarction Am J Cardiol 33 572, 1974.
Shell, W E., and Sobel, B E Reply to Dr Sarnoff's letter Am J Cardiol 33 572, 1974
Scheinman M M., Thorburn D and Abbott J A Use of atropine in patients with acute myocardial infarction and sinus bradycardia Circulation 52 627 1975
Dauchot P., and Gravenstein J S Bradycardia after myocardial ischemia and its treatment with atropine Anesthesiology 44 501 1976
Warren J V., and Lewis R P Beneficial effects of atropine in the pre hospital phase of coronary care Am. J Cardiol. 37 68 1976
Redwood D R., Smith, E R., and Epstein S E Coronary artery occlusion in the conscious dog Effects of alterations in heart rate and arterial pressure on the degree of myocardial ischemia Circulation 46 323 1972
Epstein S E., Beiser G D., Rosing D R., Talano J V., and Karsh, R. B Experimental acute myocardial infarction Characterization and treatment of the malignant premature ventricular contraction Circulation 47 446 1973.
Goldstein R E., Karsh, R B., Smith E R Orlando M Norman D Farnham, G., Redwood D R., and Epstein S E. Influence of atropine and of vagally mediated bradycardia on the occurrence of ventricular arrhythmias following acute coronary occlusion in closed-chest dogs Circulation 47 1180 1973
22. Kent K M., Smith E R Redwood D R and Epstein S E Electrical stability of acutely ischemic myocardium Influences of heart rate and vagal stimulation Circulation 42 291 1973
23 Massumi, R A. Mason D T Amsterdam E A., DeMaria A. Miller R R Scheinman, M M and Zelis R. Ventricular fibrillation and tachycardia after intravenous atropine for treatment of bradycardias N Engl. J Med. 287 336 1972
24. Zipes D P and Knoebel S B Rapid rate-dependent ventricular ectopy Adverse responses to atropine-induced rate increase Chest 62 255 1972
25 Horgan J Atropine and ventricular tachyarrhythmia, J A M.A. 223 693 1973
26 Richman, S Adverse effect of atropine during myocardial infarction Enhancement of ischemia following intravenously administered atropine J.A M.A 228 1414, 1974
27 Lunde P Ventricular fibrillation after intravenous atropine for treatment of sinus bradycardia, Acta Med. Scand 199 369 1976
28 Koch Weser J Antiarrhythmic prophylaxis in ambulatory patients with coronary heart disease, Arch. Intern Med. 129 763 1972
29 Eger E I Atropine scopolamine and related compounds Anesthesiology 23 365 1962
30 Kottmeier C A. and Gravenstein J S The parasympathomimetic activity of atropine and atropine methyl bromide Anesthesiology 29 1125 1968
31 Kalser S C and McLain P L. Atropine metabolism in man Clin Pharmacol. Ther 11 214 1970
32. Morton H J V and Thomas, E T Effect of atropine on the heart rate Lancet—December 20 1958 pp 1313-1315
33 Das G Talmers F N and Weissler A. M New observations on the effects of atropine on the sinoatrial and atrioventricular nodes in man Am. J Cardiol. 36 281 1975
34 Chamberlain D A. Turner P and Sneddon J M. Effects of atropine on heart rate in healthy man Lancet—July 1 1967 pp 12 15
35 Heinekamp W J R The central influence of atropine and hypocine on the heart rate J Lab Clin. Med. 8 104 1922.
36 Hayes A H., and Parr G V S Comparison of the actions of homatropine hydrobromide and homatropine methylbromide on human heart rate Fed Proc 21 part 1 2791 1970
37 Cullumbine H McKee W H E and Creasey N H The effects of atropine sulfate upon healthy male subjects Q.J Exp Physiol 40 309 1955
38 Hayes A. H Copelan H W., and Ketchum J S Effects of large intramuscular doses of atropine on cardiac rhythm Clin Pharmacol Ther 12 482 1971
39 Averill K H and Lamb L. E Less commonly recognized actions of atropine on cardiac rhythm Am J Med. Sci. 237 304 1959
40 Stuckey J G., Pitt M and Sloman G Atropine solution administered with an automatic device in the coronary care unit Am J Cardiol 32 958 1973

Study of serum digoxin status in digitoxicity by radioimmunoassay

A Sarangi FRCP DMRT
N Tripathy MD
D Lal MD
B C Patnaik MD
A K Swain MRCP DCH
Cuttack India

The margin of safety between therapeutic and toxic doses of digitalis is not well defined and digitoxicity remains a problem in clinical practice Though the therapeutic range of serum digoxin has been worked out to be between 0 8 ng/ml and 2 ng/ml there are overlaps and nearly two thirds of the digitalized patients attending the hospital may have their serum digoxin concentration outside the therapeutic range Variation in bioavailability of the different brands of digoxin and wide variation in the patient s responses to drugs present further problems

The various symptoms and rhythm disturbances encountered in digitalized patients may in fact be due to inherent cardiac pathology though erroneously attributed to digitoxicity

Myocardial digoxin concentration has been found to bear a constant ratio to serum digoxin level in persons with normal renal functions

Radioimmunoassay has proved to be a sensitive method for estimation of serum digoxin The present study has been taken up to evaluate digoxin status by radioimmunoassay and to correlate serum digoxin level with clinical and electrocardiographic evidences of digitoxicity

Materials and methods

Forty seven patients (32 toxic 15 nontoxic control) with congestive heart failure who were on treatment with Lanoxin brand of digoxin with daily dosage of 0 25 mg to 0 75 mg were included in the study The patients were all adults admitted to S C B Medical College Hospital Cuttack during the period March 1977 to March 1978 Thirty two patients had clinical and electrocardiographic evidence of digitoxicity according to the criteria laid down by Smith and Haber Fifteen patients who had obtained optimum therapeutic benefit from digoxin therapy without any toxic features constituted the non toxic control group in the study None of the patients had renal failure Thirty six patients suffered from rheumatic heart disease six from ischemic heart disease two from hypertensive heart disease and one from each of three other categories-namely congenital pulmonary and arteriosclerotic heart disease Arteriosclerotic heart disease was diagnosed by thickened peripheral arterial wall fundoscopic findings a rim of calcification in the aortic knuckle demonstrated radiologically and by the absence of electrocardiographic evidence of ischemia All the patients were clinically assessed and investigated for routine hematological values serum protein electrolytes serum creatinine blood urea and serum calcium Serum digoxin was estimated by radioimmunoassay (RIA) using Lanoxi test Gamma kit obtained from Wellcome Reagent Ltd England The assay was repeated after the patients recovered from toxic manifestations after the withdrawal of digoxin

Blood was collected for RIA 6 hours after the last dose of digoxin and serum was separated and

From the D partment of Medicine S C B Med al Colleg Cuttack Indi

Rece ed fo publ cat on July 3 19?9
Accepted f r publ cati n Oct 9 19 9

Reprint requests D A Sa ngi, Professo f Medicine D pt of Medi i e S C B Medical Coll ge Cutta k– 53 00 Orissa India

Burroughs Wellcome & Co

000?-8 03/80/030?89 + 0500.50/0 © 1980 The C V Mosby Co



Fig 1 Scattergram showing serum digoxin concentration in Toxic Recovered Control and Simulated Toxic groups

preserved in deep refrigeration at –28° C and was assayed using Lanoxi test Gamma kit with ^{125}I digoxin The result was plotted using count rates versus concentration of standards This was used to determine the concentration of the digoxin sample obtained from patients The data were statistically analyzed

Observation

All 47 patients (32 toxic 15 nontoxic control) were adults in an age group of 15 to 64 years Toxicity was evenly distributed in all the age groups Male to female ratio was 2 6 1 Out of 47 patients 15 had relief of symptoms without any evidence of toxicity Thirty two patients were digitoxic The clinical features of toxic patients included nausea vomiting anorexia abdominal pain lassitude and various arrhythmias (Table IA and Table IB) Seven patients out of these 32 cases were in fact in a state of underdigitalization as was subsequently revealed by RIA These seven patients were designated as a simulated toxic but under digitalized (STUD) group

The biochemical parameters such as serum protein sodium potassium creatinine calcium and blood urea are summarized in Table II

The mean serum digoxin levels in toxic and nontoxic patients were 2 64 ± 0 68 ng /ml and 1 35 ± 0 45 ng /ml respectively After recovery from the toxicity the mean serum digoxin concentration dropped to 1 43 ± 0 2 ng /ml This was significantly lower than the level in toxic patients (P < 0 001) and was similar to the

Table IA Clinical presentation of digitoxicity in 32 cases

Clinical presentation	*No of cases*	*Per centage*
Nausea	20	62.5
Anorexia	16	50
Vomiting	19	59 4
Epigastric pain	3	9 4
Excessive fatigue	1	3 1
Bradycardia	2	6 2
Irregular pulse (Pulsus bigeminus multiple ectopics AF and others)	32	100

patients in the nontoxic range (scattergram) The mean serum digoxin concentration in simulated toxic but under digitalized patients (STUD) was 0 74 ± 0 35 ng /ml This value when compared to that of nontoxic patients was significantly lower (P < 0 01) The symptoms in patients of simulated digitoxicity (STUD) were in fact due to uncontrolled congestive heart failure which subsided with increasing dosage of digitalis (Table III)

Serum digoxin concentration was dose related When dosage schedule and serum digoxin concentrations were analyzed in toxic and nontoxic patients there was significant correlation (P < 0 001) (Table IV)

All the patients had their serum creatinine and blood urea levels within the normal range (serum creatinine 0 7 to 2 mg per cent and blood urea 20 to 50 mg per cent) The value between 40 and 50 mg percent though in excess of normal has been taken as the upper limit of the normal range in our study in patients who showed no other clinical and laboratory evidences of renal dysfunction Those with higher normal values of serum creatinine and blood urea had a higher serum digoxin concentration Seven cases who had serum creatinine more than 1 5 mg /dl and blood urea more than 40 mg /dl had their serum digoxin concentration 3 3 ± 0 72 ng /ml In 18 toxic cases with serum creatinine less than 1 5 mg /dl and blood urea less than 40 mg /dl the serum digoxin concentration was 2 3 ± 0 44 ng /dl (P < 0 001 T = 4 1)

Digitoxicity was attained at a lower concentration in hypokalemic patients Six toxic patients with serum potassium less than 3 5 mEq /l had serum digoxin concentration 2 ± 0 1 ng /ml

Table IB Electrocardiographic abnormalities in 32 cases of toxic patients

Category No	*Rhythm*	*No of cases*	*Percentage*
1	1 H B	4	12.5
2	1 H B with supraventricular ectopic	1	3.1
3	Ventricular bigeminy	3	9.4
4	1 H B with ventricular bigeminy	4	12.5
5	1 H B with ventricular trigeminy	1	3.1
6	Multiple ventricular ectopic	2	6.2
7	Multi focal ventricular ectopic	3	9.4
8	PAT with varying degree of H B	2	6.2
9	AF with multifocal ventricular ectopic	1	3.1
10	Sinus tachycardia	1	3.1
11	Sinus bradycardia	2	6.2
12	Mobitz type II H B	1	3.1
13	Junctional escape rhythm	1	3.1
14	A F	6	18.8

Abbreviations H B = heart block PAT = paroxysmal atrial tachycardia A F = atrial fibrillation

Table II Mean concentration of biochemical parameters in 47 cases

	Nontoxic	*STUD group —7 cases*	*Toxic—25 cases*
Serum protein (gm/dl)	6.2 ± 0.4	6.05 ± 0.33	6.1 ± 0.44
Serum Na (mEq/L)	139.3 ± 2.5	140 ± 4.78	137.9 ± 4.1
Serum K (mEq/L)	4.2 ± 0.6	4.14 ± 0.19	3.8 ± 0.57
Serum creatinine (mg/dl)	0.75 ± 0.2	0.75 ± 0.2	0.9 ± 0.48
Blood urea (mg/dl)	30.1 ± 10.4	32.1 ± 10.9	46.5 ± 12.1
Serum calcium (mg/dl)	10.3 ± 0.5	10.3 ± 0.37	10.2 ± 0.6

STUD = simulated toxic und-digitalized group

Table III Serum digoxin concentration in simulated toxic group (STUD) before and after increase in dosage of digoxin in 4 cases

Case no	*Before increasing the dose (ng/ml)*	*After increasing the dose (ng/ml)*
17	0.4	1.6
20	0.3	1.2
21	0.5	1.8
22	0.7	1.7

In the other three cases repeat digoxin levels could not be done

Nineteen toxic patients with serum potassium value more than 3.5 mEq/L had the mean digoxin concentration 2.83 ± 0.97 ng/ml ($P < 0.05$)

No significant correlation could be established between serum digoxin and serum sodium and calcium

Routine estimation of hematological values and serum protein carried out in these patients revealed a low average nutritional status

Table IV Mean serum digoxin concentration in relation to different dosage schedule

	Serum digoxin level in ng/ml			
	Nontoxic	*Toxic*	*t*	*p*
Dosage—0.25 to 0.5 mg/day				
No of cases	7	10		
Mean ± S D	0.91 ± 0.18	2.06 ± 0.28	9.58	0.001
Dosage—0.5 to 0.75 mg/day				
No of cases	8	15		
Mean ± S D	1.14 ± 0.22	3.03 ± 0.59	6.19	0.001

Discussion

Estimation of serum digoxin before during and after recovery from digitoxicity showed that serum digoxin concentration was highest during toxicity Serum concentration higher than therapeutic range is necessary to produce digitoxicity There was no correlation of arrhythmia with mean serum digoxin concentration contrary to

Table V Serum digoxin concentrations in various studies (nontoxic and toxic patients) in ng/ml

Authors	Method	*Mean concentration* Nontoxic	Toxic	*Statistical significance*
Smith Butler and Haber[4] (1969)	RIA	1.3	3.3	Yes
Grahame Smith and Everest (1969)	86 Rb uptake	2.4	5.7	Yes
Smith & Haber[5] (1970)	RIA	1.4	3.7	Yes
Chamberlain et al (1970)	RIA	1.4	3.1	Yes
Oliver Parker and Parker (1971)	*RIA*	*1.6*	*3.0*	Yes
Hoeschen and Proveda (1971)	RIA	0.8 1.3	2.8	Yes
Fogelman et al. (1971)	RIA	1.4	1.7	No
Evered and Chapman (1971)	RIA	1.38	3.36	Yes
Beller et al (1971)	RIA	1.0	2.3	Yes
Bertler and Redfors (1971)	86 Rb uptake	0.9	2.4	Yes
Butler (1972)	RIA	1.5	2.8	Not stated
Whiting et al (1973)	RIA	0.8	3.2	Yes
Carruthers et al. (1974)	RIA	1.4	2.76	Yes
Singh et al. (1975)	RIA	2.3	3.9	Not stated
Calesnick & Dinah (1976)	RIA	1.84	3.4	Yes
Present study (1978)	RIA	1.3 ± 0.45	2.6 ± 0.68	Yes ($p < 0.001$, $t = 6.8$)

the observations of Smith and Haber[5] They observed significantly higher levels of serum digoxin in supraventricular tachycardia with block than in atrial fibrillation

In the present series seven patients diagnosed to be toxic on clinical and electrocardiographic ounds were actually nontoxic Their serum ncentration was low and they improved with a higher dosage of digitalis This observation emphasizes the value of correlating the clinical picture with serum digoxin concentration for distinguishing the real from the simulated digitoxic state

There was some overlap in serum digoxin levels among toxic and nontoxic groups The range of serum digoxin in the nontoxic group was 0.5 ng/ml to 1.8 ng/ml and in the toxic group it was 1.6 ng/ml to 4.1 ng/ml Only two patients in the toxic group had a serum level below 1.8 ng/ml Ten out of 25 toxic cases had serum concentration more than a mean concentration of 2.6 ng/ml

The mean serum concentration in digitoxicity in the present series has been compared with the findings of other workers [1] (Table V) Singh and associates have found a mean toxic level at 3.9 ng/ml The low average nutritional status and body weight may explain the lower mean values in our patients

Renal impairment hastens the process of digitoxicity by retarding the excretion of digoxin In this study serum creatinine blood urea and serum digoxin are positively correlated The greater the value of serum creatinine and blood urea the higher was the serum digoxin concentration in digitoxic patients This finding is in accord with the observations of Beller and colleagues.[6]

Digitoxicity in the present study has occurred at a lower serum concentration in hypokalemic patients Hypokalemia renders the patients more sensitive to digoxin and narrows down the margin of safety so that even in therapeutic concentrations of digoxin toxic symptoms become manifest There is a positive correlation between the serum digoxin level and serum potassium The lower the serum potassium the lower the serum digoxin level at which toxicity develops

The serum digoxin concentration in the present study has been found to be dose related (Table IV) This observation is consistent with the findings of Carruthers and co workers[1] and of Beller and associates[6]

Four cases of ischemic heart disease showed toxic features at a lower concentration (1.7 ng/ml to 3 ng/ml) which may be due to increased sensitivity of the damaged myocardium This observation supports the findings of earlier workers [4] The present study shows that undernutrition hypokalemic status and cardiac decompensation due to ischemic heart disease are the

conditions in which the margin of safety between the therapeutic and toxic range of serum digoxin concentration is narrowed down so that toxicity ensues at a lower dose level Higher normal values of serum creatinine and blood urea even in the absence of renal failure are associated with a hyper digoxinemic state and digitoxicity This situation is often encountered in digitalized patients who are on diuretics and restricted fluid intake

To conclude there is a great variability between the serum concentration of digoxin and toxic manifestations When both clinical and electrocardiographic findings are correlated with serum digoxin concentration giving due weight to etiopathology of the cardiac condition the therapeutic dose range can be distinguished from the toxic and under digitalized state

Serum digoxin estimation by RIA serves as a useful procedure not merely for detection of digitoxicity but for ensuring optimal therapeutic response and for forestalling toxic effect by appropriate adjustment of dosage

Summary

Forty seven patients who were being treated with digoxin in a daily dose range of 0 25 mg to 0 75 mg were the study material Thirty two patients were toxic Seven patients out of these 32 were in an under digitalized state and 15 patients were nontoxic All patients were clinically assessed and investigated for routine hematological value serum protein electrolytes serum creatinine blood urea and serum calcium

Serum digoxin concentration was estimated in all cases by the radioimmunoassay method The assay was repeated after the patients recovered from toxic manifestations on withdrawal of the digoxin The mean serum digoxin level in toxic patients (2 64 ± 0 68 ng /ml) was significantly higher ($P < 0\,001$) than that in nontoxic patients (1 35 ± 0 45 ng /ml) After recovery from toxicity the mean serum digoxin level (1 43 ± 0 32 ng /ml) was found to be significantly lower than the level in the toxic patients and was similar to the level in patients of the nontoxic group Seven patients whose symptoms simulated digitoxicity were in fact in an under digitalized state (0 74 ± 0 35 ng /ml) and their symptoms were relieved with a higher dosage of digoxin In this study an attempt has been made to show the importance of the estimation of serum digoxin in the assessment of therapeutic and toxic effects of the drug so as to modify the dosage schedule for the optimal therapeutic response

The authors express their gratitude to Prof B B Tripathy *Superintendent of S C B Medical College Hospital, and to* Prof M Khadanga the Principal of the Medical College

REFERENCES

1 Carruthers S G Kelly J G and McDevitt D G Plasma digoxin concentration in patients on admission to hospital Br Heart J 36 707 1974
2 Singh R B Rai H N Dube P K, Srivastav D K, *Somein P N, and Katiyar B C Radioimmunoassay of* serum digoxin in relation to digoxin intoxication Br Heart J 37 619 1975
3 Doherty J E The clinical pharmacology of digitalis glycosides—A review Am J Med Sci 255 38 1968
4 Smith T W Butler V P Jr and Haber E Determination of therapeutic and toxic serum digoxin concentration by radioimmunoassay N Engl J Med 281 1212 1969
5 Smith T W and Haber E Digoxin intoxication—the relationship of clinical presentation of serum digoxin concentration J Clin Invest 49 23 7 1970
6 Beller G A Smith T W Abelmann W H, Haber E, and Hood W B Jr Digitalis intoxication N Engl J *Med* 284 989 1971
7 Chamberlain D, Alwhite R. J., Howard M R., and Smith, T W Plasma digoxin concentration in atrial fibrillation Br Med J 3 429 1970
8 Evered D C and Chapman C Plasma digoxin concentration and digoxin toxicity in hospital patients Br Heart Journal 33 450 1971
9 *Grahame Smith, D G and Everest M S Measure*ment of digoxin in plasma and its use in diagnosis of digoxin intoxication Br Med. J 1 286 1969
10 Fogelman A M Lamont J T Finkenstein S., Rado E and Pearca H L Fallibility of plasma digoxin in differentiating toxic from nontoxic patients Lancet 2 27 1971
11 *Oliver G C Parker B M., and Parker C W Radioim*munoassay for digoxin technic and clinical applications Am J Med 51 186 1971
12 Calesnick B and Dina A Improved micro radioimmunoassay of digoxin in serum with use of I labelled digoxin Clin Chem. 20 903 19 6
13 Butler V P Assays of digitalis in the blood Progr Cardiovasc Dis 14 5 1 19 2
14 Whiting B Summer J K, and Goldberg A An assessment of digoxin radioimmunoassay Scott Med J 18 69 19 3
15 Hoeschen R J, and Proveda V Serum digoxin by radioimmunoassay Can Med Assoc J 105 170 1971
16 Bertler A, and Redfors, A Plasma levels of digoxin in relation to toxicity *Acta Pharmacol.* 29 281 1971

Electrocardiographic changes in cerebrovascular hemorrhage

Beverly J Yamour M D
M R Sridharan M D
John F Rice, M D
Nancy C Flowers M D
Louisville Ky

Patients with central nervous system disorders often have abnormal electrocardiograms in the absence of known organic heart disease Burch Myers and Abildskov were the first to report electrocardiographic abnormalities in patients with cerebrovascular accidents Since then many reports have appeared in the literature This study was done utilizing information obtained by computerized tomography (CT scan) to verify and localize the site of the hemorrhage for purposes of correlation of the hemorrhagic event with the abnormalities noted on the electrocardiogram

Materials and methods

A total of 186 patients records representing all cases with cerebral hemorrhage documented by CT scan at the University of Louisville Affiliated Hospitals from July 1977 to March 1979 were reviewed All patients were scanned on the EMI CT 1010 dedicated brain scanner in the University Hospital Most patients were examined on an emergency basis because of rapid neurological deterioration and received an unenhanced scan only Those patients who were enhanced received 60 ml of Renografin 60 followed by 300 cc of Reno M D IP All patients with evidence of any preexisting heart disease were excluded Particular care was focused on eliminating any patient from the study with evidence of atherosclerotic heart disease including angina pectoris or myocardial infarction those with ischemic changes during resting or exercise electrocardiograms and those with hypertension congenital valvular, or cardiomyopathic heart disease Patients under treatment with any cardiac drugs were excluded Only patients whose earlier electrocardiograms were normal were included for the study Electrolyte profiles were a requisite for inclusion The following report is of 65 such patients Criteria for electrocardiographic diagnosis were those reported summarized by Cooksey and colleagues[5]

This is a report then, of 65 patients with cerebrovascular hemorrhage who had no evidence of prior cardiac abnormalities drug or reasons for electrolyte effect abnormalities on their electrocardiogram

Results

The regions of CT scan abnormality were grouped as deep cerebral superficial cerebral and posterior fossa The groups were further divided by etiology The superficial cerebral group was subgrouped into traumatic and spontaneous divisions No history of prior trauma was present in either the deep cerebral or posterior fossa groups Age and sex of each group are also shown (Table I)

From the Division of Cardiology Department of Medicine University of Louisville School of Medicine Louisville Ky

This research was supported by National Institutes of Health Grants HL-19768 and HL-1[illegible] and by a grant from the Veterans Administration.

Received for publication Aug 6 1979

Accepted for publication Sept 14 1979

Reprint requests Beverly J Yamour M D Resident Dept of Internal Medicine University of Louisville School of Medicine Louisville Ky 40202.

0002-8703/80/030294 + 0[illegible]/0 © 1980 The C V Mosby Co

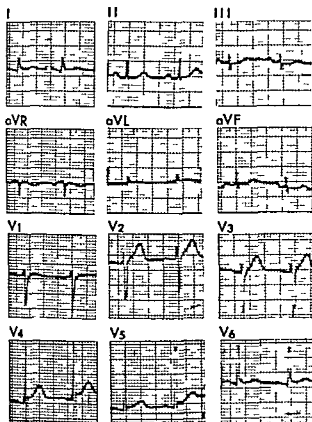


Fig 1A ECG obtained two years (February 15 19") prior to the present illness is normal.

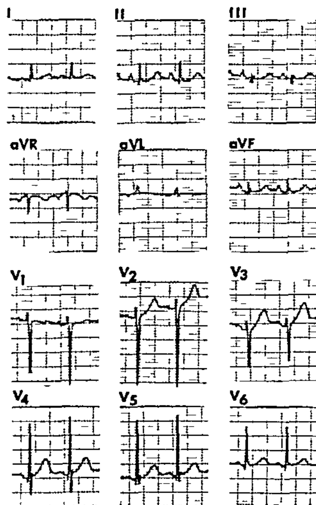


Fig 1B ECG obtained hortly after admission (February 13 19"9) shows a sinus tachycardia of about 120 beats per minute

Table I Regions of hemorrhage with numbers of patients by age and sex

	Number of patients	Mean age (range)	Sex	
			Male	Female
Deep cerebral				
A Basal ganglia	8	6? (50-89)	5	3
B Thalamus	5	6[illegible] (53 [illegible]6)	2	3
Superficial cerebral traumatic				
A Frontal	6	32 (16-69)	6	0
B Temporal parietal	10	27 (21 [illegible]8)	9	1
C Occipital	0			
Nontraumatic				
A Frontal	6	52 (34-68)	3	3
B Temporal parietal	20	63 (14-85)	10	10
C Occipital	2	(55-83)	1	1
Posterior fossa				
A Brain stem	8	53 (20-63)	[illegible]	1
B Cerebellar hemisphere	1	56 56	0	1

Sinus tachycardia was commonly seen occurring in all categories but was never seen in the majority of patients in any group (Table II)

Sinus bradycardia was less commonly seen and occurred with traumatic frontal lobe hemorrhage (33%) and nontraumatic temporal parietal hemorrhage (10%)

Sinus arrhythmia occurred in 33% of patients with traumatic frontal lobe lesions

The sudden onset of atrial fibrillation seemed only associated with hemorrhage into the brain stem area (25%) The ventricular response rate was always rapid ranging from 130 to 180

Supraventricular tachycardia occurred in 33% of the group with traumatic frontal lobe hemorrhage

Atrioventricular block of first degree occurred

Electrocardiographic changes in cerebrovascular hemorrhage

Beverly J Yamour, M D
M R Sridharan M D
John F Rice M D
Nancy C Flowers M D
Louisville Ky

Patients with central nervous system disorders often have abnormal electrocardiograms in the absence of known organic heart disease Burch Myers and Abildskov[1] were the first to report electrocardiographic abnormalities in patients with cerebrovascular accidents Since then many reports have appeared in the literature[2-7] This study was done utilizing information obtained by computerized tomography (CT scan) to verify and localize the site of the hemorrhage for purposes of correlation of the hemorrhagic event with the abnormalities noted on the electrocardiogram

Materials and methods

A total of 186 patients records representing all cases with cerebral hemorrhage documented by CT scan at the University of Louisville Affiliated Hospitals from July 1977 to March 1979 were reviewed All patients were scanned on the EMI CT 1010 dedicated brain scanner in the University Hospital Most patients were examined on an emergency basis because of rapid neurological deterioration and received an unenhanced scan only Those patients who were enhanced received 60 ml of Renografin 60 followed by 300 cc of Reno M D IP All patients with evidence of any preexisting heart disease were excluded Particular care was focused on eliminating any patient from the study with evidence of atherosclerotic heart disease including angina pectoris or myocardial infarction those with ischemic changes during resting or exercise electrocardiograms and those with hypertension congenital, valvular or cardiomyopathic heart disease Patients under treatment with any cardiac drugs were excluded Only patients whose earlier electrocardiograms were normal were included for the study Electrolyte profiles were a requisite for inclusion The following report is of 65 such patients Criteria for electrocardiographic diagnosis were those reported summarized by Cooksey and colleagues[8]

This is a report then of 65 patients with cerebrovascular hemorrhage who had no evidence of prior cardiac abnormalities drug or reasons for electrolyte effect abnormalities on their electrocardiogram

Results

The regions of CT scan abnormality were grouped as deep cerebral superficial cerebral and posterior fossa The groups were further divided by etiology The superficial cerebral group was subgrouped into traumatic and spontaneous divisions No history of prior trauma was present in either the deep cerebral or posterior fossa groups Age and sex of each group are also shown (Table I)

From the Division of Cardiology Department of Medicine University of Louisville School of Medicine Louisville Ky

This research was supported by National Institutes of Health Grants HL-19768 and HL-16901 and by a grant from the Veterans Administration.

Received for publication Aug 6 1979

Accepted for publication Sep 14 1979

Reprint requests Beverly J Yamour M D Resident Dept of Internal Medicine, University of Louisville School of Medicine Louisville Ky 40202

PVCs	*LAFB*	*LAE*	*LVE*	*NSST T*	*QT*	*Neurogenic T*	*IMI*	*U waves*	*PE*
					33				
				33	(	50			
10	10	20	15	50			10	15	
				50					
									37.5
						100			

and one with near reversion to baseline (February 22 1979) (Figs 1 A B, C and D) CT scan (Fig 2) performed the day of admission showed increased uptake overlying the pituitary secondary to aneurysmal rupture of the anterior communicating artery confirmed by cerebral arteriography

Discussion

Abnormal electrocardiograms occurring with acute cerebrovascular events have been previously described[5-12] The incidence of ECG changes in a group of subarachnoid hemorrhages was 71 5% described by Kreus and associates In groups with intracerebral hemorrhage and unclassified cerebrovascular accidents the figures of 57 1% and 41 1% have been reported In this group 80% (52 patients) had some change from their earlier electrocardiogram

What then are the possible causal relationships that could explain the presence of electrocardiographic abnormalities in patients suffering from a variety of acute intracranial disease?

Kaye McDonald and Randall have demonstrated that subendocardial hemorrhages are an uncommon finding after prolonged and intense sympathetic activity on the heart Such a condition of intense sympathetic drive is to be expected during the terminal stages of acute intracranial hemorrhages However actual myocardial damage that can be detected pathologically is unusual and the vast majority of cases brought to autopsy have revealed a normal heart

Direct stimulation of various areas of the brain is known to result in abnormal electrical patterns of the heart Stimulation of the frontal lobes the orbital cortex the anterior part of the temporal lobe the insula and the angulate gyrus commonly produces alterations in ST segment duration and amplitude as well as changes in the T wave duration Areas where stimulation is associated with ventricular ectopy and aberration of ventricular conduction are primarily found in the limbic lobe the hypothalamus and the central gray matter Cropp and Manning[3] have suggested that lesions of area 13 on the orbital surface of the frontal lobe may be responsible for the ECG changes Poole has written on the induction of arrhythmias and ST segment and T wave changes in the ECG during manipulation of the circle of Willis in man

A variety of abnormalities of depolarization and cardiac automaticity are seen with stimulation of both cortical and subcortical areas

Stimulation of the stellate ganglia produces consistent abnormalities of repolarization of the ventricular myocardium In the work in dogs by Yanowitz and associates right stellate ganglionectomy with intact left stellate or left stellate stimulation resulted in T waves of increased area and prolonged QT intervals in 45 of 45 dogs

Left stellate ganglionectomy with an intact right stellate or stimulation of the right stellate ganglion produced a significant T wave inversion less often in 14 of 35 dogs Removal of the

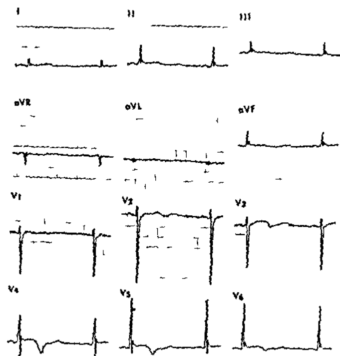


Fig 1C ECG obtained on February 19 1979 shows repolarization abnormalities which began *shortly after* the ECG taken on February 13 and which *were maximal* on February 19 Sinus bradycardia at about 40 beats per minute was also present

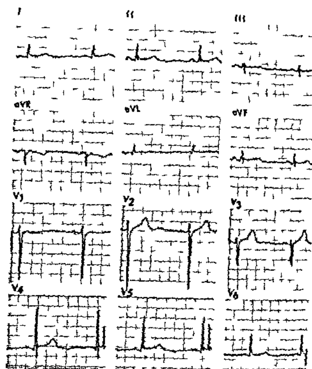


Fig 1D Three days following (February 2? 1979) the previous tracing except for sinus bradycardia with associated U waves the electrocardiogram has returned essentially to normal

ganglion also produced abnormalities Removal the right ganglion resulted in refractory period longation on the anterior surface of the left ventricle Left stellate ganglionectomy produced refractory period prolongation on the posterior surface of the left ventricle

The vagus nerve influences the heart s sinus node by phase related pulses of discharge If repetitive bursts of vagal impulses arrive at certain phases of the cardiac cycle the sinus node will become very unstable and a severe sinus arrhythmia will occur At other phases of the *cardiac* cycle vagal stimulation serves to stabilize the *sinus node* In this instance the slow rate of discharge results in a marked but regular bradycardia

In addition to the vagal influence some ECG changes are mediated through the sympathetic pathway Porter and associates were able in cats to produce T wave inversion by stimulation in the central hippocampus The T wave inversion could be blocked by transection of the cervical spinal cord interrupting sympathetic fibers In humans strong cortical connection exist between the hypothalamus and the orbito frontal cerebral cortex by way of the fronto hypothalamic pathway which allows hypothalamic efferents to reach the various autonomic tegmental nuclei whose cell bodies connect to the sympathetic cell bodies in the thoraco lumbar gray matter[3] A complete pathway for sympathetic outflow then exists from the cerebral cortex especially the orbito frontal area to the heart via the stellate ganglia

In this retrospective study of 65 patients there seemed to be a high incidence of electrocardiographic abnormalities in frontal lobe hemorrhages both spontaneous and traumatic compared to hemorrhages in other areas Neurogenic T waves were frequently seen only in frontal lobe lesions (50%) The sudden onset of atrial fibrillation in association with brain stem hemorrhages was noted in 25% of the cases

We conclude that neurologically induced ECG abnormalities are frequent in anterior cerebral events Further the sudden development of electrocardiographic abnormalities in the setting of anterior cerebral or brain stem hemorrhage suggests consideration of a cerebral association rather than a primary myocardial event



Fig 2 CT scan shows a focal hemorrhage between the two frontal lobes anterior to the third ventricle secondary to a subsequently documented anterior communicating artery aneurysm *(arrow)*

Summary

The electrocardiographic abnormalities found in localized cerebrovascular hemorrhage which have been documented by computerized tomography (CT) scans are described Frontal lobe hemorrhages are associated especially with the electrocardiographic abnormalities of QT prolongation and neurogenic T waves Brain stem hemorrhage seems to be associated with non cardiogenic pulmonary edema and sudden development of atrial fibrillation It is proposed that the cause of ECG abnormalities in association with lesions in the vicinity of area 13 on the orbital surface of the frontal lobe or around the circle of Willis results from alterations in sympathetic and parasympathetic tone mediated by fibers from the orbito frontal area to the heart via the stellate ganglia

REFERENCES

1 Burch, G E Myers R and Abildskov J A A new electrocardiographic pattern observed in cerebrovascular accidents Circulation 9 19 1954
2 Cherian G Vijayaraghwan G and Abraham J Electrocardiogram in stroke A report of 205 cases Indian Heart J 25(Suppl) 230 19 3
3 Cropp G J and Mannin G W Electrocardiographic change simulating myocardial ischemia and infarction associated with spontaneous intracerebral hemorrhage Circulation 22 25 1960
4 Hunt D, McRae C and Zupf P Electrocardiographic and serum enzyme changes in subarachnoid hemorrhage AM HEART J 77 4 9 1969
5 Kreus K E Kamila S J, and Takala J R Electrocardiographic changes in cerebrovascular accidents, Acta Med Scand 185 327 1969
6 Srivastava S C and Robson A O Electrocardiographic abnormalities associated with subarachnoid hemorrhage Lancet 2 431 1964
7 Fentz V, and Gormsen J Electrocardiographic patterns in patients with cerebrovascular accidents Circulation 25 22 1962
8 Cooksey J D et al Clinical Electrocardiography and Vectorcardiography Chicago 19 7 Year Book Medical Publishers Inc
9 Estanol B V, and Marin O S Cardiac arrhythmias and sudden death in subarachnoid hemorrhage Stroke 6(4) 38 1975
10 Surawicz B Electrocardiographic pattern of cerebrovascular accidents J A M A 197(11) 191 1966
11 Harrison M T and Gibb B H Electrocardiographic changes associated with a cerebrovascular accident Lancet 2 429 1964
12 Kaye M P, McDonald R H and Randall W C Systolic hypertension and subendocardial hemorrhages produced by electrical stimulation of the stellate ganglion Circ Res 9 1164 1961
13 Warrur C B C Subha K U Ravirdran K N and Parameswaren K The electrocardiogram in strokes J Assoc Physicians India 19 71 1971
14 Yanowitz F, Preston J B and Abildskov J A Possible role of unilateral changes in sympathet-

the production of neurogenic electrocardiographic abnormalities, Circulation (Suppl 31-32) October 1965
15 Levy M N, Martin P J Iano T and Zieske J Paradoxical effect of vagus nerve stimulation on the heart rate in dogs Circ Res 25 303 1969
16 Levy M N Iano T, and Zieske H Effects of repetitive bursts of vagal activity on the heart rate Circ Res 30 186 1972
17 Levy M N Neural mechanisms in cardiac arrhythmias J Lab Clin Med 90 599 1977
18 Poole J L Vasocardiac effects of the circle of Willis Arch Neurol Psychiatr 78 355 1957
19 Porter B W, Kamikawa K, and Greenhost J H persistent electrocardiographic abnormalities experimentally induced by stimulation of the brain Am Heart J 64 815 1962
20 Delgago J M R Circulary effects of cortical stimulation Physiol Rev 40(Suppl 4) 146 1960
21 Joff E C, Kell J F, Jr and Carroll M N Jr Effects of cortical stimulation and lesions on cardiovascular function Physiol Rev 43 68 1963
22 Carroll M N Jr Hoff E C Kell J F Jr and Suter C G The effects of ethanol and chlordiazepoxide in altering autonomic responses evoked by isocortical and paleocortical stimulation Biochem Pharmacol 8 15 1961
23 Holkman C H, Mauck H P Jr and Hoff E C ECG changes resulting from cerebral stimulation Am Heart J 71 695 1966
24 Levine H D Non specificity of electrocardiogram associated with coronary artery disease (Phi Chi Lecture) Am J Med 15 344 1953
25 Beatue J Brown G R and Long C N H The hypothalamus and the sympathetic nervous system Res Publ Assoc Res Nerv Ment Dis 9 249 1930
26 Fuster J M and Weinburg S J Prelectrical changes of the heart cycle induced by stimulation of diencephalic regions Exp Neurol 2 96 1969
27 Hockman C H Mauck H P Jr and Hoff E I ECG changes resulting from cerebral stimulation Am Heart J 71 695 1966
28 Manning J W, Jr and Peiss C N Cardiovascular responses to electrical stimulation in the diencephalon, Am J Physiol 198 366 1960
29 Mauck H P Jr and Hockman C H Central nervous system mechanism medicating cardiac rate and rhythm, Am Heart J 74 96 1967
30 Cayaffa J The autonomic nervous system Cook County Graduate School of Medicine 19 4
31 Hersch C Electrocardiographic changes in subarachnoid hemorrhage meningitis and intracranial space occupying lesions Br Heart J 26 785 1964

Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978 Therefore all manuscripts must be accompanied by the following written statement signed by one author The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C V Mosby Company in the event the work is published The undersigned author warrants that the article is original is not under consideration by another journal and has not been previously published I sign for and accept responsibility for releasing this material on behalf of any and all co authors Authors will be consulted when possible regarding republication of their material

The pediatric spectrum of dynamic left ventricular obstruction

Thomas Riggs, M.D.
Stephen Hirschfeld, M.D.
Hooshang Rajai, M.D.
Cleveland, Ohio

The original descriptions of hypertrophic subaortic stenosis (IHSS) have been associated with echocardiographic features of asymmetric hypertrophy of the interventricular septum (ASH), abnormal systolic anterior motion of the mitral valve (SAM), and midsystolic aortic valve closure.[1] A unified concept of IHSS as an autosomal dominant disease characterized by ASH and disorganized myocardial histology has been proposed.[2] When subaortic obstruction was present, both SAM and midsystolic aortic closure were frequently found.[3-5]

Recently, the specificity of ASH and SAM as indicators of IHSS has been challenged. ASH has been demonstrated in many types of congenital heart disease.[6] SAM without ASH has been found in patients with and without concentric myocardial hypertrophy who have associated intraventricular pressure gradients. Several patients with SAM have been found to have a mid ventricular pressure gradient or left ventricular cavity obliteration rather than subaortic obstruction. Both SAM and midsystolic closure of the pulmonic valve have been associated with dynamic left ventricular outflow obstruction in patients with D transposition of the great arteries.[11]

Echocardiographic and hemodynamic features similar to that seen in adults with IHSS have been reported in association with systemic hypertension, aortic stenosis, coarctation of the aorta, and a variety of other congenital heart diseases. Most reports have concentrated on an adult population. This study evaluated a population of pediatric patients over a four year period to evaluate the diverse clinical presentations, echocardiographic findings, and hemodynamic data that are associated with dynamic left ventricular outflow obstruction. Furthermore, an attempt was made to identify the pathophysiologic mechanisms that might lead to this obstruction.

Patients and methods

The study group comprised 21 pediatric patients with classic echocardiographic signs of subaortic obstruction (or subpulmonic in patients with D TGA) and/or cardiac catheterization documented dynamic left ventricular obstruction at our institution from 1975 through 1978. The patients were divided into three groups based on their age at presentation. Nine patients were evaluated during the first month of life and were designated *Group A* (neonates). Six patients presented between four months and two years of age and were called *Group B* (infants). The remaining six patients were eight to 17 years of age and were designated Group C (children and adolescents) (Table I).

Among the Group A patients, four were infants of diabetic mothers, two had idiopathic hypertension, one had hypertension from coarctation of the aorta, one had tetralogy of Fallot, and the remaining neonate had idiopathic hypertrophic cardiomyopathy. The diagnoses in the six Group B patients were: coarctation of the aorta (1), D transposition of the great arteries (4), and

From Case Western Reserve University School of Medicine, Department of Pediatrics and Rainbow Babies and Children's Hospital, Cleveland, Ohio.

Received for publication Sept. 6, 1979.

Accepted for publication Nov. 9, 1979.

Reprint requests: Thomas Riggs, M.D., Pediatric Cardiology Division, Rainbow Babies and Childrens Hospital, 2101 Adelbert Rd., Cleveland, Ohio 44106.

Table I Echocardiographic and catheterization data on the 21 pediatric patients comprising the study population

Patient no	Diagnosis	Age	Treatment	*Echo data*						*Catheteri ation data*				
													L PSG	
				IVS	*LVW*	*IVS LVW*	*RVW*	*SAM*	*MSC*	*RVP*	*LVP*	*R PSG*	*Basal*	*Provocable*
1	IDM	1 d	None	1 2	0 6	2 0	0 4	+	+	ND	ND	ND	ND	ND
		25 d	None	0 7	0 4	1 75	0 4	+	–	ND	ND	ND	ND	ND
2†	IDM	1 d	Digoxin	1 4	0 6	2 33*	0 6	+	+	ND	ND	ND	ND	ND
3	IDM	1 d	None	0 9	0 3	3 0	0 6	+	–	ND	ND	ND	ND	ND
4	IDM	2 d	None	1 1	0 5	2 2	0.2	+	+	ND	ND	ND	ND	ND
		33 d	None	0 6	0 3	2 0	0 2	–	–	ND	ND	ND	ND	ND
5	HT	3 d	Digoxin	0 3	0 3	1 0	0 3	–	–	ND	ND	ND	ND	ND
		3 wk	Prop	0 5	0 3	1 67	0 4	–	–	110	110	ɩ0	20	40
6†	Idio	4 d	Digoxin	0 7	0 5	1 29	0 4	+	+	55	100	0	20	ND
		3 wk	Prop	0 7	0 4	1 40	0.3	+	+	ND	ND	ND	ND	ND
7	CoA	3 wk	None	0 9	0 6	1 50	0 3	+	+	40	170	15	30	ND
		18 m	Digoxin	0 6	0 5	1 20	0 2	–	–	ND	ND	ND	ND	ND
8	HT	3 wk	Prop	0 8	0 7	1 14	0 7	+	+	50	100	0	0	°5
	NT	6 m	Prop	0 4	0 4	1 00	0 3	–	–	ND	ND	ND	ND	ND
9	TOF	1 m	None	0 4	0 3	1 33	0 5	+	+	90	90	NA	0	ND
		1 vr	None	0 5	0 6	0 84	0 6	+	+	100	100	NA	0	ND
10	CoA	7 m	None	0 9	0 7	1 29	0 4	+	+	100	200	45	60	ND
11	IHSS	2 y	None	ND	ND	ND	ND	ND	ND	9ɔ	°00	65	100	ND
	S/P myec	7 y	Prop	1 8	1 5	1.20	0 4	+	+	44	180	14	60	ND
12	D TGA	5 m	S/P BAS	0 4	0 3	1 33	0 5	+	+	100	60	0	30	ND
13	D TGA	ɔ m	S/P BAS	0 3	0 4	0 75	0 5	+	+	90	40	0	2ɔ	ND
14	D TGA	5 m	S/P BAS	0 5	0 4	1 20	0 5	+	+	85	50	0	25	ND
15	D TGA	5 m	S/P BAS	0 4	0 3	1 33	0 5	–	+	110	65	0	35	ND
16	IHSS	8 y	None	ND	ND	ND	ND	ND	ND	30	230	0	130	ND
	S/P myec	14 y	Prop	1.5	0 9	1 67	0 4	+	+	30	120	0	20	90
17	Conc	10 y	Prop	1.2	1 5	0 80	0 3	+	+	30	13ɔ	0	0	110
	Conc	12 y	None	0 8	0 8	1 00	0 3	–	–	ND	ND	ND	ND	ND
		13 y	None	1.2	1 1	1 09	0 3	–	–	28	130	0	0	1°0
		14 y	Prop	1 1	1 1	1 00	0 4	–	–	ND	ND	ND	ND	ND
19	IHSS	13 y	None	ND	ND	ND	ND	ND	ND	24	136	0	40	1°0
	S/P myec	18 y	Prop	2 0	1 6	1 25	0 4	+	+	3°	180	0	60	ɩ0
20	IHSS	16 y	None	ND	ND	ND	ND	ND	ND	53	145	2ɔ	20	100
		20 y	Prop	2 0	1 1	1 82	0 3	+	+	85	190	60	60	120
21	IHSS	17 y	None	1 6	0 8	2 00	0 3	+	–	ND	ND	ND	ND	ND

Abbreviations and symbols ASH = asymmetric septal hypertrophy BAS = balloon atrial septostomy CoA = coarctation of the aorta Conc = concentric left ventricular hypertrophy d = age in days D TGA = D transposition of the great arteries HT = systemic hypertension Idio = idiopathic IDM = infant of a diabetic mother IHSS = idiopathic hypertrophic subaortic stenosis IVS = interventricular septum L PSG = peak systolic pressure gradient left side LVP = peak left ventricular systolic pressure LVW = left ventricular posterior wall m = age in months MSC = mid systolic aortic closure Myec = myectomy NA = does not apply ND = not done NT = normotensive Prop = propranolol R PSG = peak systolic pressure gradient right side RVP = peak right ventricular systolic pressure RVW = right ventricular anterior wall SAM = systolic anterior motion of the mitral valve S P = status-post TOF = tetralogy of Fallot wk = age in weeks yr = age in years + = present – = absent

*Value outside normal

†Patient died

IHSS (1) Among the Group C patients four had IHSS and two had concentric left ventricular hypertrophy None of the Group C patients had hypertension coarctation of the aorta or aortic stenosis

All patients had echocardiographic examinations which were performed with commercially available ultrasound transducers ultrasonoscopes and strip chart recorders Measurements of the right ventricular anterior wall (RVW) of the interventricular septum (IVS) and left ventricular posterior wall (LVPW) were made at the onset of the electrocardiographic QRS complex in the plane of the tips of the mitral valve leaflets in older patients and in the plane of the posterior mitral valve leaflet in infants and neonates (Fe

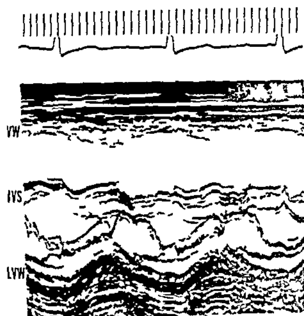


Fig 1 This echocardiogram is from a patient with D transposition of the great arteries and demonstrates systolic anterior motion of the mitral valve (patient No 14) IVS = interventricular septum LVW = left ventricular posterior wall RVW = right ventricular anterior wall

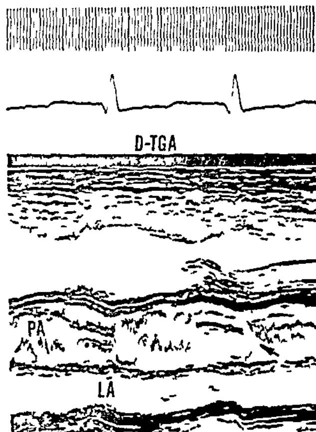


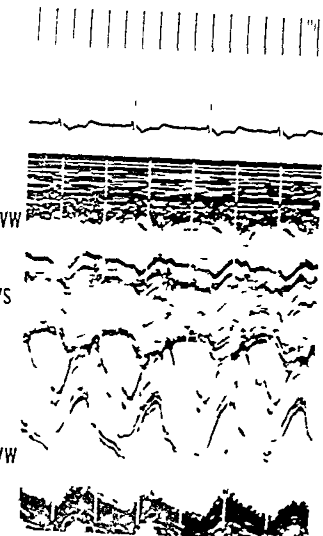
Fig 2 This echocardiogram is also from patient No 14 and shows the systolic flutter and mid systolic closure *(denoted by the arrow)* which implies subpulmonic obstruction This infant had a subpulmonic gradient of 25 mm Hg *D-TGA* = D transposition of the great arteries *LA* = left atrium *PA* = pulmonary artery

genbaum s transducer positions 1 and 2 respectively)[6,11] Care was taken to visualize the right side of the IVS as this may be confused with the tricuspid valve annulus Two independent observers measured the echocardiograms to the nearest 1 0 mm and the values for each measurement are the average of those determinations

Measurements greater than normal as defined by Rogé and associates study[1] were considered abnormal and an IVS/LVPW ratio equal to or greater than 1 5 was considered to indicate asymmetric septal hypertrophy[6] Systolic anterior motion of the mitral valve was diagnosed after recording the mitral valve below the level of the mitral annulus and observing rapid anterior motion and return Both aortic valve leaflets (pulmonic leaflets in patients with D transposition) were visualized in order to observe mid systolic closure

Most patients underwent cardiac catheterization The exceptions were four infants of diabetic mothers (IDMs) and one asymptomatic adolescent with IHSS Infants less than two months of age received no premediation while older patients received either diphenhydramine hydrochloride (1 mgm /kg) and droperidol (0 1 mgm /kg) or meperidine hydrochloride (1 mgm /kg) and hydroxyzine hydrochloride (1 mgm /kg) Further sedation or anesthesia was achieved when necessary with intravenous ketamine hydrochloride (1 mgm /kg) diazepam (0 1 mgm /kg) or diphenhydramine hydrochloride (1 0 mgm /kg) Standard right and left heart catheterizations were performed and all pressures were recorded prior to angiography The left ventricular pressures were recorded with a multiple hole catheter in an attempt to prevent spurious elevation of pressures by catheter entrapment When the left ventricle was approached through the aortic valve a pigtail catheter (Cook Inc) was used

An attempt was usually made to provoke or to amplify a left ventricular aortic pressure gradient with post ectopic beats isoproterenol infusion or supine exercise Propranolol was sometimes given in an attempt to lessen the left ventricular aortic gradient Angiographic assessment of the right and left ventricles was performed in all patients who underwent cardiac catheterization If isopro



3 The echocardiogram is from patient No 19 and ... trates a marked increase in thickness of the interven... ular septum and posterior left ventricular wall. The ... ent had a family history of IHSS and had undergone a ... ectomy several years before this examination IVS = inter... tricular septum LVW = left ventricular posterior wall ... W = right ventricular anterior wall

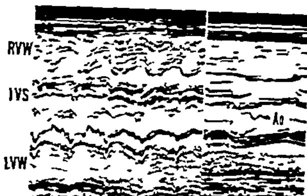


Fig 4 This composite echocardiogram is from patient No 8 who was a hypertensive neonate There is severe hypertrophy of the right ventricular wall, interventricular septum, and left ventricular wall. In addition there is systolic anterior motion of the mitral valve and midsystolic closure of the aortic valve. These abnormalities all resolved by six months of age while the patient was receiving propranolol Ao = aorta IVS = interventricular septum LVW = left ventricular posterior wall RVW = right ventricular anterior wall.

...enol had been used then at least 30 minutes ...psed between the cessation of isoproterenol ...d performance of angiography so that the ...rt rate could return to the basal level

...sults

...nical

...oup A—Neonates Among the nine neonates in ... study eight presented with mild to severe ...gestive heart failure Four patients were ...ted with digoxin prior to establishing a defini... diagnosis and two of these died one despite ...ontinuation of the digoxin and the adminis...tion of propranolol The seven surviving neo...s improved with propranolol (2), digoxin (1) ...no medical therapy (4) The patient with tetralogy of Fallot became increasingly cyanotic and had a Blalock Taussig shunt at one year of age

Group B—Infants Six infants presented for evaluation of a cardiac murmur (patients No 10 and 11) or for increasing cyanosis (patients No 12 to 15) None had congestive heart failure The infants with D transposition all underwent a successful Mustard procedure while the infant with IHSS underwent a myectomy All patient are currently well

Group C—Children and Adolescent Six children in this group presented for evaulation of a cardiac murmur and were either asymptomatic or had mild exercise intolerance Two were treated with both surgery and propranolol three with propranolol alone and one received no treatment

Echo data (Table I)

Group A The LVPW thickness was increased in four of nine patients The IVS was thicker than normal in eight of nine neonates with an elevated IVS/LVW ratio in six patients The RVW thickness was increased in four patients Seven patients had SAM and six of these seven had midsystolic closure of the aortic valve

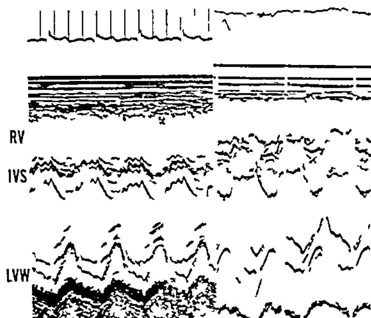


Fig 5 These echocardiograms are from patient No 18 and demonstrate the development of concentric left ventricular hypertrophy over a two year period *IVS* = interventricular septum *LVW* = left ventricular posterior wall *RV* = right ventricle

Group B The LVPW and IVS were each increased in two infants the IVS/LVW ratio was elevated in only one patient The RVW was thick in the four infants with D transposition All patients showed mid systolic closure and five demonstrated SAM (Figs 1 and 2)

Group C The LVPW was increased in four patients while all patients demonstrated a thick IVS (Fig 3) The IVS/LVW ratio was elevated in four cases The RVW was normal in all patients There was SAM in five patients with accompanying mid systolic closure in four of these cases

Sequential echo data Sequential echocardiograms were available from seven neonates (Group A) Five survivors demonstrated resolution of hypertrophy and signs of subaortic obstruction The most striking example (patient No 8) had a normal echocardiogram by six months of age (Fig 4) Two older infants (Group B) had sequential echocardiograms which continued to show SAM and midsystolic closure Sequential studies were available from one child in Group C whose concentric left ventricular hypertrophy progressed over a two year period (Fig 5)

Catheterization data

Group A Four patients in this group who underwent cardiac catheterization had a left ventricle aortic pressure gradient at rest or with provocation which ranged from 20 to 40 mm Hg This gradient could be ablated with propranolol in patient No 5 (Fig 6) Three neonates had a right ventricle pulmonary artery gradient in one case this was attributable to tetralogy of Fallot Angiography demonstrated myocardial hypertrophy and deformity of the left and right ventricular cavities with encroachment of the right ventricular outflow tract in two cases (no 5 and 7) with a right ventricular pulmonary artery gradient

Group B Two of the infants in Group B had a left ventricle to aorta gradient of 60 mm Hg while the remaining four infants with D transposition had subpulmonic gradients ranging from 25 to 35 mm Hg The angiograms from patients No 10 and 11 showed myocardial hypertrophy with deformity of the left and right ventricular cavities Infant No 10 showed left ventricular cavity obliteration during systole The four infants with D transposition each had a large right ventricle with a small left ventricle and narrowing of the subpulmonic region during ventricular systole

Group C Five of the six patients in this category had cardiac catheterization studies and all of these had left ventricle aorta pressure gradients at rest or with provocation Two patients with concentric hypertrophy (No 17 and 18) had no gradient at rest but developed large gradients (110 and 120 mm Hg) during isoproterenol infusions (Fig 7) Only one patient in Group C had a right

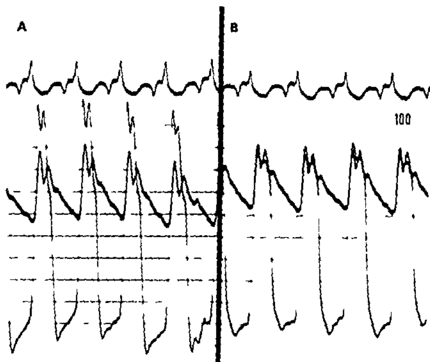


Fig 6 These pressure tracings were obtained before *(panel A)* and after *((panel B)* the administration of intravenous propranolol to patient No 5 The left ventricle and aortic pressure curves are displayed and the pressure gradient of 20 mm Hg *(left panel)* was ablated with propranolol *(right panel)* Each horizontal line represents 10 mm Hg

ventricle pulmonary artery pressure gradient Angiography showed typical features of IHSS in three patients and systolic left ventricular cavity obliteration in the two cases with concentric LV hypertrophy (Fig 8)

Discussion

Many different anatomic and physiologic cardiac states may result in echocardiographic and hemodynamic findings that are similar to IHSS The spectrum of dynamic left ventricular obstruction in children appears even broader than in adults because of the addition of neonatal abnormalities (e g infants of diabetic mothers) and congenital cardiac diseases The two adolescents in this series with concentric left ventricular hypertrophy and cavity obliteration are younger than patients in other reports and represent the first documentation of this entity in the pediatric age group Furthermore the infant in this series with tetralogy of Fallot and signs of left ventricular obstruction is unique

We believe the term hypertrophic obstructive cardiomyopathy is appropriate to describe a constellation of hemodynamic echocardiographic and angiographic findings which occur with dynamic left ventricular obstruction The most common of these disorders is IHSS but other patients have hypertrophic cardiomyopathy that can be attributed to one or several predisposing factors These factors include encroachment of the left ventricular cavity or its outflow tract altered hemodynamics of left ventricular ejection myocardial hypertrophy increased afterload and genetic predisposition Subaortic obstruction can be attributed to SAM of the mitral valve and to posterior bulging of the septum into the left ventricular outflow tract while myocardial hypertrophy may encroach on the left ventricular cavity Altered ventricular ejection hemodynamics have been suggested as the primary event in hypertrophic cardiomyopathy [8] The increased velocity of ejection through the left ventricular outflow tract may exacerbate the narrowing of this structure through the Venturi effect [9] Myocardial hypertrophy either as a primary disorder or secondary to increased left ventricular overload contributes to the encroachment of the left ventricular cavity and to enhancement of its contractility Finally a genetic predisposition is strongly associated with the development of IHSS or with the occurrence of hypertrophic cardiomyopathy in rarer syndromes such as Noonan's syndrome Pompe's

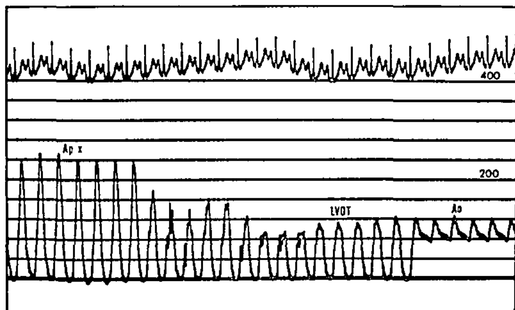


Fig 7 This pressure tracing is from patient No 18 who had concentric left ventricular hypertrophy While there was no left ventricular aortic pressure gradient at rest a gradient of 1?0 mm Hg could be induced with isoproterenol or with supine exercise Each horizontal line represents 40 mm Hg *Ao* = ascending aorta *Apex* = left ventricular apex *LVOT* = left ventricular outflow tract

disease or Friedreich s ataxia [3, 4]

Among our patients several had familial IHSS or idiopathic concentric left ventricular hypertrophy while for other patients we could propose a mechanism for their hypertrophic cardiomyopathy The patients with hypertension or coarctation of the aorta had a left ventricular pressure load with resultant concentric hypertrophy rather than ASH An association between coarctation of the aorta[19] or fixed left ventricular outflow obstruction[7] and hypertrophic cardiomyopathy has been noted previously in pediatric patients Hypertrophic cardiomyopathy secondary to systemic hypertension is rare in our experience and is unusual in adult patients Systemic hypertension in neonates may more frequently lead to hypertrophic cardiomyopathy than in adults perhaps related to the neonate s propensity for developing ASH and his disordered myocardial cell architecture[2] The latter may also have contributed to the myocardial hypertrophy in the infants of diabetic mothers or their hypertrophy may be secondary to glycogen deposition *in utero* from chronic hyperinsulinemia and hyperglycemia Our infants of diabetic mothers did not undergo cardiac catheterization but others have shown a subaortic gradient in these infants [1] The infant in this series with tetralogy of Fallot is unusual and may represent a chance association The development of ASH secondary to right ventricular hypertrophy has been demonstrated in patients with tetralogy of Fallot but hypertrophic obstructive cardiomyopathy has not been documented However our patient had SAM midsystolic closure an unusual left ventricular angiogram and no ASH The absence of a left ventricle to aorta pressure gradient may be related to the large ventricular septal defect in the subaortic position

Previous studies [22] *have pointed out the echo* cardiographic features of dynamic subpulmonic obstruction in infants with D transposition of the great arteries and an intact ventricular septum The dilation of the right ventricle may contribute to the narrowing of the left ventricular outflow tract The systolic anterior motion of the mitral valve and the systolic fluttering of the pulmonic valve may be secondary to the Venturi effect and to altered left ventricular geometry [11] Infants with D transposition and intact ventricular septum who develop increasing cyanosis despite an adequate interatrial defect or who demonstrate hypercyanotic spells (similar to those seen in tetralogy of Fallot) may have dynamic left ventricular outflow obstruction

In summary the pediatric spectrum of hypertrophic obstructive cardiomyopathy has been illustrated in 21 patients Echocardiography,

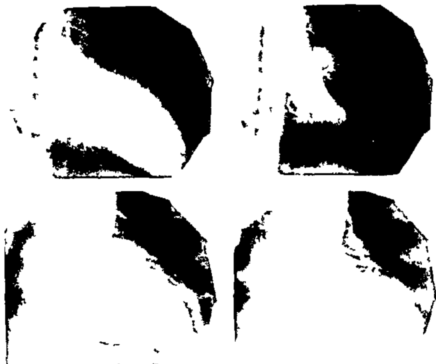


Fig 8 This composite photograph shows end diastolic *(left)* and end systolic *(right)* frames from cineangiography obtained from patients No 17 *(top row)* and No 18 *(bottom row)* The top row were obtained in an RAO projection while the bottom row were obtained in a PA projection Each set of angiograms demon trated systolic cavity obliteration of the left ventricle

extremely useful in identifying left ventricular outflow obstruction or myocardial hypertrophy he use of digitalis is probably contraindicated in ese patients since this may exacerbate or create obstruction to outflow from the left ventricle Further experience with hypertrophic cardiomyopathy and awareness of its coexistence with congenital heart disease may help elucidate the pathophysiologic mechanisms of this disorder

Summary

Twenty one pediatric patients with echocardiographic and/or hemodynamic evidence of dynamic left ventricular obstruction are presented in order to examine the pathophysiologic mechanisms of this disorder Neonates commonly had transient hypertrophic cardiomyopathy related to hypertension or to being infants of diabetic mothers Infants with D transposition of the great arteries sometimes developed signs of sub pulmonic dynamic obstruction Older children and adolescents had either classic findings of IHSS or concentric left ventricular hypertrophy The spectrum of hypertrophic cardiomyopathy appears to be broader in pediatric patients than in adults

The authors wish to thank Ms Monica Stelmach for her help in preparing this manuscript

REFERENCES

1 Menges H Jr Brandenburg R O and Brown A L Jr The clinical hemodynamic and pathologic diagnosis of muscular subvavular aortic stenosis Circulation 24 1126 1961
2 Henry W L Clark C E and Epstein S E Asymmetric septal hypertrophy Echocardiographic identification of the pathognomonic anatomic abnormality of IHSS Circulation 47 225 1973
3 Henry W L Clark C E and Epstein S E Asymmetric septal hypertrophy (ASH) The unifying link in the IHSS disease spectrum Circulation 47 827 1973
4 Rossen R M Goodman D J Ingham R E and Popp R L Echocardiographic criteria in the diagnosis of idiopathic hypertrophic subaortic stenosis Circulation 50 747 1974
5 Krajcer Z Orzan F Pechanek L W Garcia E and Leachman R D Early systolic closure of the aortic valve in patients with hypertrophic subaortic stenosis and discrete subaortic stenosis Am J Cardiol 41 8 1 1978
6 Larter W E Allen H D Sahn D J and Goldberg S J The asymmetrically hypertrophied septum Further differentiation of its causes Circulation 53 19 19 6
7 Maron B J Gottdiener J S Roberts W C Henry W C Savage D D and Epstein S E Left ventricular outflow tract obstruction due to systolic anterior motion of the anterior mitral leaflet in patients with concentric left ventricular hypertrophy Circulation 57 5 10 9
8 Mintz G S Kotler M N Segal B L and Parry W

R Systolic anterior motion of the mitral valve in the absence of asymmetric septal hypertrophy Circulation 57 756 19 8
9 Raizner A E Awdeh M R and Chahine R A Clinical correlates of left ventricular cavity obliteration Am J Cardiol 40 303 1977
10 Come P C Buckley B H Goodman Z D Hutchins G M Pitt B and Fortuin N Hypercontractile cardiac states simulating hypertrophic cardiomyopathy Circulation 55 901 1977
11 Aziz K U Paul M H and Muster A J Echocardiographic assessment of the left ventricular outflow tract in D transposition of the great arteries Am J Cardiol 41 543 19 8
12 Bloom K R Meyer R A Bore K E and Kaplan S The association of fixed and dynamic left ventricular *outflow obstruction* AM HEART J 89 586 1975
13 Feigenbaum H Echocardiography Philadelphia 19 2 Lea & Febiger Publishers pp 29-34
14 Rogé C L L, Silverman N H Hart P A and Ray R M Cardiac structure growth pattern determined by echocardiography Circulation 57 285 1978
15 Somerville J and Becu L Congenital heart disease associated with hypertrophic cardiomyopathy Br Heart J 40 1034 19 8
16 Rees, A Elbl F Minhas K and Solinger R Echocardiographic evidence of outflow tract obstruction in Pompe s di ea e (glycogen storage disease of the heart) Am J Cardiol 37 1103 1976
17 Smith E R Sangalang V E Heffernan L P Welch J P and Flemington C S Hypertrophic cardiomyopathy The heart disease of Friedreich s ataxia AM HEART J 94 428 1977
18 Ehlers K H Engle M A Levin A R and Deely W J Eccentric ventricular hypertrophy in familial and sporadic instances of 46 XX XY Turner phenotype Circulation 45 639 1972
19 Fiddler C I Tajik A J Weidman W H McGoon D C Ritter D G and Giuliani E R Idiopathic hypertrophic subaortic stenosis in the young Am J Cardiol 42 93 19 8
20 Bulkley B H Weisfeldt M L and Hutchins G M Asymmetric septal hypertrophy and myocardial fiber *disarray features of normal developing and malformed* hearts Circulation 56 292 19
21 Gutgesell H P Mulline C F Gillette P C Speer M Rudolph A and McNamara D G Transient hypertrophic subaortic steno is in infants of diabetic mothers J Pediatr 89 120 19 6
22 Aziz K U Paul M H Idris I S Wilson A D Muster A J Clinical manifestations of dynamic left ventricular outflow tract stenosis in infants with D tran po ition of the great arteries with intact ventricular septum Am J Cardiol 44 290 1979

The usefulness of radionuclide ventriculography for the identification and assessment of patients with coronary heart disease

Joseph Lindsay, Jr., M.D.
Nicholas G. Nolan, M.D.
Steven A. Goldstein, M.D.
James M. Bacos, M.D.
Washington, D.C.

Coronary arteriography and left ventricular angiography are often necessary to identify accurately the presence of coronary atherosclerotic heart disease and to assess its severity. As yet no noninvasive technique provides information of similar quality.

Recently, cardiac imaging employing radionuclides has received considerable attention as a tool for identifying and evaluating coronary disease. When combined with exercise this approach appears particularly promising.[1, 2] Studies utilizing 201 Thallium, which, like its analogue potassium, is taken up by myocardium in porportion to blood flow, have been most widely employed. Segments of relative hypoperfusion may be identified by detection of areas of reduced radioactivity within the myocardium.[3] An equally promising technique employs imaging of the left ventricular blood pool. An accurate representation of the left ventricle may be acquired using a computer interfaced scintillation camera during the first passage of a radioisotope through the heart or following equilibration of the radioactivity within the blood pool. The latter images are gated by means of an electrocardiographic signal and reconstructed in various formats including left ventricular cineangiography.

Borer and associates[1, 4] and other investigators have used rest and exercise radionuclide left ventriculography to demonstrate differences between the response of the left ventricle to exercise in normal persons and in patients with ischemic heart disease. As is the case during contrast left ventriculography, segmental contraction abnormalities are often present during the radionuclide examination.[1, 5] Further, segments which contract normally at rest may become abnormal during exercise. In addition to segmental abnormalities of left ventricular function, an abnormal response of the global ejection fraction may be detected. In contrast to normal subjects in whom the ejection fraction increases with exercise, it characteri...

Table 1. Normal coronary arteriograms and normal left ventricle: clinical features

Age	26-59, mean = 4[illegible] years; 16 (84%) older than 39 years
Sex	9 men, 10 women
Reason for catheterization	
Chest pain (one had "Prinzmetal syndrome")	17
Ventricular fibrillation	1
Abnormal exercise ECG	1
Complicating conditions	
Mitral valve prolapse	8
Hypertension	3
Alcoholism	2
Diabetes	1

From the Departments of Medicine and Nuclear Medicine, The George Washington University School of Medicine and the Washington Hospital Center, Washington, D.C.

Received for publication Sept. [illegible], 197[illegible].

Accepted for publication Nov. [illegible], 197[illegible].

Reprint requests: Joseph Lindsay, M.D., Director, [illegible] Laboratory, Dept. of Cardiology, Washington Hospital Center, [illegible] Irving St., NW, Washington, D.C. [illegible]

0002-8703/80/030310 + 09$00.90/0 © 1980 The C. V. Mosby Co.

Table II Patients with occlusive coronary disease

	Number	*Age*		*Sex*		*Angina*	*Myocardial infarction*
		Range	*Mean*	*Male*	*Female*		
One vessel	15	31-68	54	10 (67%)	5 (33%)	13 (87%)	3 (20%)
LAD	10	42-68	53	6	4	9	1
RCA	4	31-68	53	3	1	3	1
CIRC	1	62		1	0	1	0
Two vessel	20	31-71	53	19 (95%)	1 (5%)	15 (75%)	13 (65%)
LAD+RCA	10	31-67	51	10	0	8	9
LAD+CIRC	9	38-71	56	9	0	6	3
RCA+CIRC	1	57		0	1	1	1
Three vessel	41	36-72	56	34 (83%)	7 (17%)	36 (88%)	24 (59%)
Total	76	31-72	55	63 (83%)	13 (17%)	65 (85%)	40 (53%)

cally fails to rise or declines in patients with coronary or left ventricular disease.

The present study was undertaken to examine the usefulness of multiple gated acquisition of the left ventricular blood pool as a clinical tool for the identification of individuals with ischemic heart disease and for estimation of the severity of the disease process. Our experience with the technique when offered as a clinical service forms the basis for this analysis.

Methods

Multiple gated acquisition of the left ventricular blood pool has been offered as a clinical service in the nuclear medicine laboratory of this hospital since late 1977. Exercise examinations were made available in March 1978. Approximately 1300 patients have been examined to date.

This analysis concerns the first 100 patients to undergo rest and stress examinations who (1) had coronary arteriography within six months of the study (within one month in 85%), (2) did not have valvular heart disease, (3) had not had cardiac surgery, and (4) did not have clinical myocardial infarction between arteriography and the radionuclide examination.

Nineteen patients had normal coronary arteriograms and normal left ventricular cineangiograms. Eight of this number had mitral valve prolapse but none had more than slight mitral regurgitation. Table I describes the clinical features of these patients.

Seventy six individuals had a 50% or greater occlusion of at least one coronary artery. The distribution of these lesions is indicated in Table II along with certain clinical features of the patients.

Five patients had abnormal catheterization studies but lacked 50% occlusion of a coronary artery. Four had abnormal left ventricular cineangiograms. The remaining patient had typical pain of ischemic heart disease, several less than 50% occlusions of the left anterior descending and circumflex coronary arteries, and dramatically reduced velocity of flow through the partially occluded arteries and an adjacent apparently normal diagonal branch. The clinical, angiographic, and radionuclide findings in these five patients are outlined in Table III.

Radionuclide angiography. Blood pool visualization was achieved by in vivo labelling of the patient's erythrocytes with 20 millicuries of 99m technetium using 1.7 milligrams of stannous pyrophosphate as the mordanting agent. Scintigraphic data were collected with a General Electric Porta Camera II C or with a G. E. Data Camera fitted with a high sensitivity parallel hole collimator. A hard wired "zoomer" and a cardiac shield were employed in the more recently performed studies. The cameras were interfaced to either an Informatek Simis III or IVB Computer. All patients were studied in the supine position using the left anterior oblique projection. The exact placement of the camera was individually chosen for each patient so as to best visualize the interventricular septum. This usually required an angle of 42 to 48 degrees. A 15 degree caudal inclination was employed so as to separate the left atrium from the left ventricle. In order to achieve maximal reproducibility between the resting and stress phases of the examination, particular care was exercised to position the patient optimally with respect to the bicycle ergometer prior to the beginning of the study and not to move the patient between the two phases of the examination.

Table III Abnormal patients with less than 50% coronary occlusions

Age/sex	Clinical problems	Catheterization findings	Radionuclide ventriculogram
1 49M	Atypical chest pain Atrial fibrillation	Normal coronary arteries Diffuse hypokinesis of LV	Mild diffuse hypokinesis EF fell from 0 51 to 0 50
2 53F	Atypical chest pain Hypertension	Normal coronary arteries Segmental hypokinesis of LV	Abnormal segmental wall motion, EF rose from 0.59 to 0 61
3 60M	Atypical chest pain PVCs	30% occlusion RCA Segmental hypokines s of LV	Abnormal segmental wall motion, EF fell from 0 ₀8 to 0 46
4 41M	CHF	Normal coronary arteries Severe diffuse hypokinesis of LV	Severe diffuse hypokinesis EF fell from 0 17 to 0 09
5 51M	Typical effort angina	<50% occlusions in LCA and CIRC "slow flow" in LAD and a diagonal	Mild hypokinesis appeared with stress EF fell from 0 68 to 0 60

Table IV Maximum level of exercise attained

	No	Watts	Heart rate	Double product
Nl CA/Nl LV	11	56 ± 8	108 ± 7	181 ± 15
Nl CA/MVP	8	43 ± 6	106 ± 6	202 ± 16
Occlusive CAD				
One vessel	15	43 ± 9	106 ± 5	182 ± 11
Angina or ST	9	28 ± 8	102 ± 6	166 ± 11
No angina or ST	6	60 ± 14	111 ± 7	204 ± 21
Two vessel	20	53 ± 6	98 ± 4	153 ± 9
Angina or ST	10	50 ± 8	97 ± 5	163 ± 12
No angina or ST	10	56 ± 10	103 ± 6	145 ± 14
Three vessel	41	40 ± 3	100 ± 3	161 ± 7
Angina or ST	18	36 ± 4	98 ± 4	149 ± 8
No angina or ST	23	46 ± 5	101 ± 5	170 ± 14

Pavel and associates modification[11] of the multiple ECG gated equilibrium data acquisition and processing technique of Borer and colleagues[3,4] was utilized This involves the computer generation of 16 composite image matrices representing a single cardiac cycle Each frame of this series contains the spatial isotopic distributional information describing the configuration of the blood pool during a specific phase of the cardiac cycle Images of high statistical quality are obtained by collecting these data from many individual cycles and by programming the computer to create a series of multiple exposures This series of images is displayed sequentially on the computer screen so as to simulate a beating heart From the counts contained within the left ventricular end systolic and end diastolic regions of interest the computer calculated the ejection fraction

Following placement of the ECG leads and an IV line the patient was allowed to reach a baseline state with respect to pulse and blood pressure When this was achieved the resting phase of the examination was started This involved the collection of a total of ten million counts and required approximately seven minutes

Upon completion of this acquisition period patients were exercised in the supine position by means of a bicycle ergometer (Warren E Collins Braintree MA) The electrocardiographic signal (usually a modified Lead II) was displayed continuously on an oscilloscope Strip chart recordings were obtained at intervals and whenever significant changes were observed Blood pressure was measured during each minute of exercise by means of a sphygmomanometer Exercise was begun at 25 watts (150 kilopond meters/minute) and increased by that amount every two minutes until the subject began to manifest fatigue angina or electrocardiographic signs of ischemia Data acquisition was then initiated and continued for three minutes during which the patient continued to pedal Angina or progressive ST depression necessitated reduction in the workload prior to completion of the three minutes in some In five it was necessary to terminate exercise during the final 30 to 60 seconds of data acquisition Table IV indicates the level of exercise attained Half of the patients with occlusive coronary disease had angina ST depression or both during exercise

Each computer generated left ventricular cineangiogram was reviewed independently by two of us (J L and N G N) without knowledge of the catheterization findings Disagreement in the assessment of regional wall motion was resolved by joint review often with reference to computer generated isocount lines which assist in the delineation of the edge of the left ventricular blood pool during various stages of the cardiac

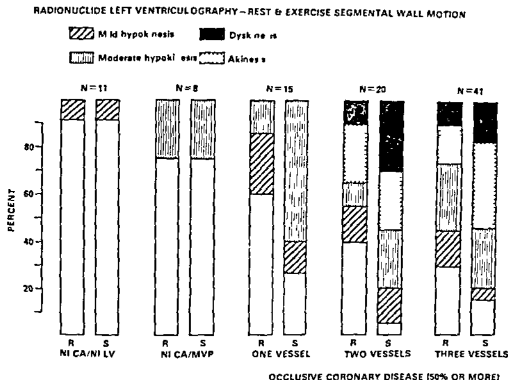


Fig 1 The bar graphs depict the per cent of patients in each diagnostic category with abnormality of segmental wall motion The degree of the abnormality is indicated by variation in shading

cycle A judgment was made regarding the contractility of septal apical and lateral (or posterior) segments A minimal abnormality was termed mild hypokinesis and a definitely hypokinetic segment was termed severe hypokinesis "Akinesis" was used in cases of failure of the segment to contract and dyskinesis when outward or paradoxic motion occurred during systole

Results

Normal coronary arteriograms and normal left ventriculograms At rest ten of these eleven (91%) patients had normal segmental wall motion slight hypokinesis was detected in one No wall motion aberrations appeared during exercise in the 10 who were normal at rest No deterioration occured in the minimally abnormal ventriculogram of the eleventh (Fig 1)

In these eleven patients the left ventricular ejection fraction ranged from 0 56 to 0 75 at rest (mean ± SEM = 0 65 + 0 02) (Fig 2 Table V) During exercise it ranged from 0 50 to 0 74 (mean ± SEM = 0 67 ± 0 02) This increase is not significant A rise in ejection fraction during exercise of three to 22% of the resting value was observed in seven patients A fall of eight to 17% of the resting value occurred in the remaining four patients (Fig 3) Two of these four were alcoholic and two were severely hypertensive The latter two were receiving 160 and 240 mg of propranolol respectively for that problem

Mitral valve prolapse At rest six of these eight (75%) patients had normal segmental wall motion Severe hypokinesis was present in the apical segment in one instance and in the apical portion of the septal segment in another During exercise regional wall motion continued to be normal in the six who had normal findings at rest A larger area of the left ventricle became hypokinetic during stress in the other two (Fig 1) Both had ischemic ST changes on the ECG during exercise and one of the two experienced anginal pain None of the six patients with normal regional wall motion had exercise induced ST abnormalities and only one had chest discomfort during stress

The left ventricular ejection fraction at rest ranged from 0.59 to 0 79 (mean ± SEM = 0 68 ± 0 03) (Fig 2) During exercise it ranged from 0 53 to 0 76 (mean ± SEM = 0 68 ± 0 03) In five of the eight the change during stress ranged from a decline of four % to a rise of two % of the resting value By contrast one had an increase of 27% one a decline of nine % and

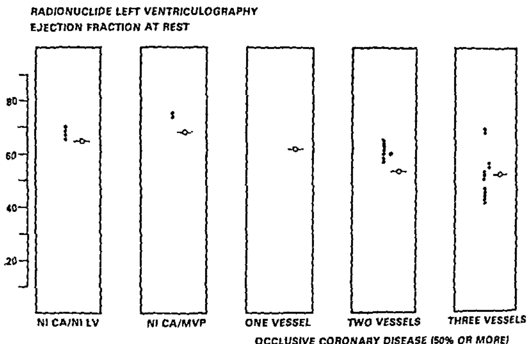


Fig 2 The resting left ventricular ejection fraction for individual patients in each diagnostic category is depicted.

Table V Left ventricular ejection fraction

	Nl CA/NL LV	NlCA/MVP	Occlusive Coronary Disease: One Vessel	Two Vessel	Three Vessel
Rest	0.65 ± 0.02	0.68 ± 0.03	0.62 ± 0.02	0.54 ± 0.03	0.52 ± 0.0?
Exercise	0.67 ± 0.02	0.68 ± 0.03	0.59 ± 0.02	0.50 ± 0.03	0.48 ± 0.03*

< 0.01
† p < 0.05
* p < 0.01

one a decline of 10% of the resting value (Fig 3)

Occlusive coronary disease

Single vessel occlusion At rest six of the 15 (40%) patients had abnormal segmental wall motion Slight hypokinesis was detected in four and severe hypokinesis was seen in the remaining two During exercise stress the contraction pattern of five of the nine with normal resting wall motion and all four with mildly abnormal patterns deteriorated Thus during stress normal segmental wall motion was present in four (27%) slight hypokinesis in two (13%) and severe hypokinesis in nine (60%) (Fig 1)

In these 15 patients the left ventricular ejection fraction at rest ranged from 0.49 to 0.74 (mean ± SEM = 0.62 ± 0.02) (Fig 2 Table V) During stress it ranged from 0.49 to 0.71 (mean ± SEM = 0.59 ± 0.02) This decline is significant ($p < 0.01$) when the paired t test is applied Three patients had a small rise in ejection fraction (four to eight % of the resting value four had no change and seven had a fall of fro[m] one to 29% of the resting value (Fig 3) A decl[ine] of at least ten % of the resting value took place [in] four (27%) all of whom had occlusion of the le[ft] anterior descending artery

Double vessel occlusion At rest twelve of [the] (60%) patients had abnormal segmental contra[c]tion Slight hypokinesis was present in three a[nd] severe hypokinesis was present in two Five ha[d] akinetic and two had dyskinetic segments Se[ven] of the eight which were normal at rest deteri[o]rated Thus during exercise stress six patien[ts] (30%) had dyskinetic segments five (25%) ha[d] akinesis five had severe hypokinesis (25%) a[nd] three (15%) had mild hypokinesis One (5[%]) remained normal (Fig 1)

In these patients the resting ejection fractio[n] ranged from 0.30 to 0.74 (mean ± SEM = 0.54 [±] 0.03) In six it was less than 0.50 (Fig 2 Table V) During exercise stress it ranged from 0.25 to 0.6[…]

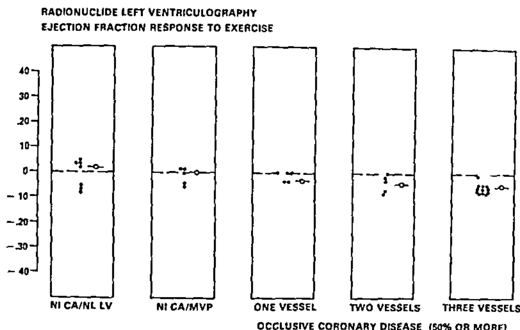


Fig 3 The response in left ventricular ejection fraction to exercise for individual patients in each diagnostic category is depicted.

(mean ± SEM = 0 50 ± 0 03) This decline is significant ($p < 0.05$) Three patients (15%) had an increase in ejection fraction during stress of eight to 17% of the resting level two (10%) had no change and 15 (75%) had a decline of from two to 29% The decline amounted to ten % or more of the resting value in nine (45%) (Fig 3)

Triple vessel occlusion At rest 29 of 41 (71%) patients with occlusive disease in all three major vessels had abnormal wall motion at rest Dyskinesis was present in four (10%) akinesis in seven (17%) severe hypokinesis was present in 12 (29%) and mild hypokinesis was present in six (15%) During exercise stress six (15%) remained normal Dyskinesis was present in seven (17%) akinesis was present in 15 (37%) severe hypokinesis appeared in eleven (27%) and mild hypokinesis was apparent in two (5%) (Fig 1)

The resting left ventricular ejection fraction in 40 patients ranged from 0 19 to 0 81 (mean ± SEM = 0 52 ± 0 02) In 17 patients (43%) this value was below 0 50 (Fig 2 Table V) One patient had a ventricular aneurysm His left ventricular silhouette exceeded the area available to the computer for the ejection fraction calculation During stress the ejection fraction in the 40 in whom it could be calculated ranged from 0 10 to 0 82 (mean ± SEM = 0 48 ± 0 03) The decline during exercise is significant ($p < 0.001$) In 12 patients (29%) a rise in ejection fraction of one to 35% of the resting value accompanied exercise and in 29 a fall of one to 65% was detected In five (13%) the increment was at least 10% of the resting value while in 17 (43%) the decrement was at least that amount (Fig 3)

Discussion

The radionuclide angiographic findings obtained in our laboratory are consistent with the experience previously reported in patients with coronary heart disease[3 7] Regional wall motion abnormal at rest in 62% became abnormal in an additional 24% so that during exercise abnormality was detected in 86% of patients Furthermore the left ventricular ejection fraction characteristically failed to rise significantly and with few exceptions fell during exercise often quite dramatically

With a single exception segmental wall motion was normal both at rest and during exercise in the 11 patients who had no angiographic abnormality of their coronary arteries or left ventricle A rise in global ejection fraction reported to be characteristic of normal individuals[3 7] was observed in seven of the 11 The lack of a normal response in four patients and the relatively small increase in several of the others probably reflects the fact that cardiac catheterization was requisite for admission to this study Thus patients whose noninvasive studies were abnormal or who had impressive signs and symptoms of heart disease

were selected for catheterization For instance of the four whose ejection fraction fell with exercise, two were alcoholic and two were severely hypertensive One of the alcoholic patients had had an episode of ventricular fibrillation and the two hypertensive subjects were receiving substantial amounts of propranalol daily

The findings in our eight patients in whom mitral valve prolapse was documented by left ventriculography are of interest Two had hypokinesis at rest which became somewhat more widespread during exercise It is noteworthy that these two individuals had ischemic ST changes during exercise None of the other six exhibited such changes Furthermore a substantial increase in the global ejection fraction was observed in only one of the eight The factors discussed above in relation to the selection for catheter study of the 11 individuals with normal coronary arteriograms and normal left ventriculograms may apply here as well Our small group is certainly not representative of the majority of patients with this disorder They were older (47 to 59 years of age) and they all had experienced chest discomfort more or less suggestive of ischemic heart disease On the other hand other investigators have encountered similar abnormalities in the radionuclide ventriculograms of patients with mitral prolapse[12,13] and left ventricular dysfunction has been frequently detected during cardiac catheterization in these patients

The specificity of the technique can not be estimated from our data Among several of our 11 patients who had normal angiographic studies there are reasons to suspect the possibility of an abnormal left ventricular myocardium as a result of hypertension drug therapy alcoholism or other causes It is encouraging that despite the presence of such factors ten of the 11 had normal regional left ventricular wall motion both at rest and during stress The single exception had a minimal abnormality Because of the manner in which our normal patients were selected it is not surprising that in four we did not find the rise during exercise of the global ejection fraction characteristic of subjects selected for study by other investigators because they were free of all signs of heart disease

As we attempted to make diagnostic decisions in individual cases we became aware of certain pitfalls Visual review of the left ventricular cineangiograms for the detection of regional wall motion abnormality requires a subjective judgment by the reviewer This is true of most radiographic and angiographic diagnostic procedures. Fortunately many cardiologists and radiologists are accustomed to studying left ventricular wall motion by means of contrast angiography We found that most abnormalities were obvious even to the inexperienced and we found that subtle changes could be recognized confidently with some experience

The use of the response to exercise of the global ejection fraction in interpretation of an individual patient s study is a more troublesome problem In order to interpret the observed response one needs to know the error of the measurement Since the difference between the rest and stress examination includes whatever inaccuracies are present in both studies the observed response to exercise is subject to a potential error as great as the sum of the errors of measurement in two examinations Thus the actual response to exercise may be exaggerated obscured or in the worse case reversed in direction Since it seems unlikely that these estimations are more accurate than ± 5% of the observed value[16,17] we have chosen to regard a change of 10% of the resting value as probably significant

In addition to errors of measurement the amount of exercise undertaken must be important in determining the amount and direction of change of the ejection fraction response The data of Borer and associates[3,4] suggests that characteristic ejection fraction changes occur during submaximal exercise but whether or not the patient with coronary disease exercises sufficiently to produce ischemia seems certain to be important Berger and associates[8] and Frischknecht and colleagues[9] found that the ejection fraction fell far more often in patients with coronary disease when exercise was adequate to produce electrocardiographic evidence of ischemia Only one of the seven coronary patients in our series who increased his ejection fraction by at least 10% of the resting value had ST changes suggesting ischemia an observation which seems to support the position that exercise to the point of ischemia is important

Brady and associates[1] recently reported that five of the six false negative examinations encountered in their study of 86 coronary patients were observed in the 15 who did not have angina or ischemic ST change and who did not reach a rate pressure product of 250 The ejection

fraction increased by an average of 0 12 in these five patients [1] Eleven of our 76 coronary patients had normal segmental wall motion during stress Six were among the 39 (15%) who were inadequately exercised by the criteria of Brady et al and five were among the 37 (14%) who were adequately stressed Although our data do not confirm Brady s experience we consider that the level of stress reached is very important It remains to be determined what level of stress is adequate to allow a confident reading of normal

The effect of the beta blocking agents on the results of this examination are also worthy of consideration Borer and associates[20] have shown that acute intravenous propranalol does not obscure the exercise induced decline of the left ventricular ejection fraction in coronary patients Wisenburg and colleagues[21] demonstrated a smaller increment in ejection fraction during bicycle exercise in normal subjects receiving oral propranalol and a smaller decrement in coronary patients during propranalol administration as compared to their peformance prior to receiving the agent Furthermore it seems likely that since administration of propranalol allows angina patients to undertake a greater amount of muscular work before the appearance of symptoms or ECG changes [22] [3] some patients will develop leg fatigue and be protected from developing ischemia by beta blockade We therefore recommend the discontinuation of propranalol before a radionuclide ventriculogram It is however often judged by the referring physician to be unsafe or impractical Therefore 41 of the 76 coronary patients in this study were receiving this agent Five of the eleven with normal segmental wall motion during stress were not receiving propranalol two were receiving 160 mg per day or more and four were receiving lesser amounts Although we postulate a protective effect from this drug our data do not establish this We do view with some skepticism a normal examination in patients receiving this agent

The radionuclide ventriculogram appears to be useful not only in identifying patients with heart disease but also as a means of assessing its severity The resting study provides insight into left ventricular function quite comparable to that obtained from contrast studies [8] [9] The response of the left ventricle to exercise appears to provide additional information regarding left ventricular reserve and the amount of left ventricle jeopardized by occlusive disease [3] Our study does not provide quantitative information in this regard but is consistent with this view An ejection fraction less than 0 50 was present in 24 (32%) of our coronary patients Twenty two of the 24 (92%) had severe occlusive disease in both the left anterior descending and in the right coronary artery Twenty (83%) had a clinical history of myocardial infraction Eight additional patients had a fall in their ejection fraction during exercise to a level below 0 50 Of those eight seven had multivessel disease A decline of at least ten % of the resting ejection fraction took place in 30 (39%) of the patients with coronary disease Of these 26 (87%) had multivessel coronary disease and the remaining four had proximal occlusive disease in the left anterior descending artery

Unfortunately a less abnormal study does not preclude severe arterial disease as estimated by coronary arteriography An increase in ejection fraction greater than ten% of the resting value and normal left ventricular wall motion were found in five of 41 (12%) of patients with occlusions of at least 50% in each of the three major branches of the coronary arteries Oddly such normal studies were not obtained in the 20 patients with two occluded vessels or in the 15 patients with single vessel disease Review of these radionuclide ventriculograms and recalculation of the ejection fraction revealed no technical errors Perhaps greater exercise stress would have disclosed latent abnormality One of the five had no vessel judged at arteriography to be occluded by as much as 75% and a second had an occlusion of such a magnitude only in the right coronary The other three had 75% or greater occlusions in multiple vessels It remains to be determined whether this apparent aberration results from an error in the performance or the interpretation of either the radionuclide ventriculogram or the coronary arteriograms or whether it identifies a small group of patients with unusually competent collateral vessels or whether there is some other explanation

Based on the experience herein reported and a total of some 1 300 examinations in our laboratory to date we feel that rest and exercise radionuclide left ventriculography is a valuable diagnostic modality for clinical application Much remains to be learned regarding its sensitivity and specificity Furthermore intriguing questions remain regarding its use in assessing the physiologic behavior of the left ventricle and the coronary circulation

Summary

To assess the usefulness of radionuclide angiography for the identification and evaluation of patients with coronary heart disease, we analyzed 100 consecutive patients who had undergone that examination and coronary arteriography

Regional wall motion abnormality during exercise was detected in 65 of 76 (86%) patients with occlusive coronary disease and in one of 11 (9%) with normal coronary arteries and normal left ventriculograms

The changes in the left ventricular ejection fraction in response to exercise were not helpful for the identification of individual patients with coronary disease since changes were often small and within the error of the technique Substantial decline of the ejection fraction during exercise indicated multivessel disease or severe proximal left anterior descending artery occlusion

REFERENCES

1 Bailey I K Griffith L S C Rouleau J Strauss H W and Pitt B Thallium 201 myocardial perfusion imaging at rest and during exercise Circulation 55 79 1977
2 Ritchie J L Trobaugh G B Hamilton G W Gould K L Narahara K A Murray J A, and Williams D L Myocardial imaging with thallium 201 at rest Circulation 56 66 1977
3 Borer J S Bacharach S L Green M V Kent K M Epstein S E and Johnston G S Real time radionuclide cineangiography in the noninvasive evaluation of global and regional left ventricular function at rest and during exercise in patients with coronary artery disease N Engl J Med 296 839 1977
4 Borer J S Bacharach S L Green M V Kent K M Johnston G S and Epstein S E Effect of nitroglycerine on exercise induced abnormalities of left ventricular regional function and ejection fraction in coronary artery disease Circulation 57 314 1978
5 Rerych S K Scholz I M Newman G E Sabiston D C and Jones R H Cardiac function at rest and during exercise in normals and in patients with coronary heart disease Ann Surg 187 449 1978
6 Berger H J Reduto L A Johnstone D E Borkowski H Sand J M Cohen L S Langau R A Gottschalk A Zaret B L and Lytlik L Global and regional left ventricular response to bicycle exercise in coronary artery disease Am J Med 66 13 1979
7 Jengo J A Oren V Conant R Brizendine M Nelson T Uszler J M and Mena I Effects of maximal exercise stress on left ventricular function in patients with coronary artery disease using first pass radionuclide angiocardiography Circulation 59 60 1979
8 Burow R D Strauss H W Singleton R Pond M Rehn T, Bailey I K Griffith L C Nickoloff F and Pitt B Analysis of left ventricular function from multiple gated acquisition cardiac blood pool imaging Circulation 56 1024 1977
9 Federman J, Brown M L Tancredi R G Smith H C, Wilson D B and Becker G J Multiple gated acquisition cardiac blood pool isotope imaging Mayo Clin Proc 53 625 1978
10 Stokely E M Parkey R W Bonte F J Graham K D Stone M J and Willerson J T Gated blood pool imaging following 99m TC stannous pyrophosphate imaging Radiology 120 433 1976
11 Pavel D G, Byrom M E Ayres B Pietras R J Bianco J A and Kanaleis C Jr Multifaceted evaluation of left ventricular function by the first transit technique using Anger H type camera and an optimal protocol correlation with biplane roentgen angiography Nuclear Cardiology Selected Computer Aspects, Proceedings of a Society for Nuclear Medicine Symposium 1978 Atlanta GA pp 129 138
12 Gottdiener J S Borer J S Bacharach S L, Green M V Kent K M Rosing D R and Epstein S E Left ventricular dysfunction in mitral value prolapse Am J Cardiol 43 367 1979
13 Akmad M Sullivan T Haibach H Sandock K Logan K and Holmes R Exercise induced changes in left ventricular function in patients with mitral valve prolapse J Nucl Med 20 640 1979
14 Gulotta S J Gulco L Padmanabhan V and Miller S The syndrome of systolic click murmur and mitral valve prolapse—a cardiomyopathy? Circulation 49 11 1974
15 Scampardonis G Yang S S Maranhao V Goldberg H and Gooch A S Left ventricular abnormalities in prolapsed mitral leaflet syndrome Circulation 48 287 1973
16 Marshall R C Berger H G Reduto L A Gottschalk A and Zaret B L Variability in sequential measures of left ventricular performance assessed with radionuclide angiocardiography Am J Cardiol 41 531 1978
17 Wackers F J Th Berger H J Johnstone D E Goldman L Reduto L A Langou R A Gottschalk A, and Zaret B L Multiple gated cardiac glood pool imaging for left ventricular ejection fraction validation of the technique and assessment of variability Am J Cardiol 43 1159 1979
18 Frischknecht J Steele P Kirch D Jensen D and Vogel R Effect of exercise on left ventricular ejection fraction in men with coronary artery disease AM HEART J 97 494 1979
19 Brady T J Thrall J H Lo K, Clare J Rogers W and Pitt B Sensitivity of exercise radionuclide ventriculography in coronary artery disease detection Importance of adequate exercise J Nucl Med 20 687 1979
20 Borer J S Bacharach S L Green M V, Rosing D R Kent K M Seides S F and Epstein S E Effects of propranalol on left ventricular function during exercise in patients with coronary artery disease Circulation 57 and 58 (Suppl II) 1151 1978
21 Wisenberg G Marshall R Schelbert H and Roe C The effect of oral propranalol on left ventricular function at rest and during exercise in normals and in patients with coronary disease as determined by radionuclide angiography J Nucl Med 20 C 9 1979
22 Gianelly R E Treister B L and Harrison D C The effect of propranalol on exercise induced ischemic ST depression Am J Cardiol 24 161 1969
23 Wolfson S and Gorlin R Cardiovascular pharmacology of propranalol in man Circulation 40 501 1969
24 Frishman W Smithen C Belfer B Kligfield P and Killip T Noninvasive assessment of clinical response to oral propranalol therapy Am J Cardiol 35 635 1975
25 Thadamu U Davidson C Singleton W and Taylor S H Comparison of the immediate effects of five β adrenoreceptor blocking drugs with different ancillary properties in angina pectoris N Engl J Med 300 750 1979

Experimental and laboratory reports

Left ventricular cavity obliteration hemodynamic behavior of the postextrasystolic beat

J A Sobrino
C Hernández Lanchas
A del Rio
I Mate
A Carrillo
M A Imizcoz
N Sobrino
Madrid Spain

In postextrasystolic beats there is an increase of myocardial contractility that leads to an increase of intraventricular and aortic pressures and to an augmented ejection[1]

Brockenbrough and associates[2] have shown that in patients with idiopathic hypertrophic subaortic stenosis (IHSS) there is a paradoxical decrease of the aortic pressure in the postextra systolic beat (PEB)

Left ventricular cavity obliteration (LVCO) is an angiographic entity characterized by a marked reduction in the ventricular cavity during contraction This entity is associated with states of "hypercontractility especially those pre senting with left ventricular hypertrophy as in idiopathic hypertrophic subaortic stenosis (IHSS) However, in some cases the ventricular hypertrophy is not prominent and the most significant feature is the hypercontractile state In this regard a similar situation has been induced in experimental dogs during inotropic stimulation and hemorrhagic shock[4]

Recently a similar behavior has been reported in the PEB in patients with LVCO without obstruction to the left ventricular outflow tract and in patients with IHSS pointing to a close similarity between the two conditions[5]

In the present work the changes in aortic and ventricular pressure in the PEB are analyzed in 13 cases of LVCO without obstruction to the left ventricular outflow tract and substantial differ ences from their behavior in IHSS are found

Material and methods

Thirteen patients six males and seven females ranging in age between 12 and 62 years (mean 37 7 years) with LVCO in their left ventriculograms were studied In 11 cases no pressure gradient could be found either in basal conditions or after amyl nitrite administration The remaining two cases showed pressure gradients of 18 and 20 mm Hg respectively after amyl nitrite In all cases roentgenographic and electrocardiographic data were analyzed Echocardiograms were available in 10 cases

The hemodynamic studies were performed with light sedation and no patient was receiving any cardioactive medication Pressures were recorded before angiography was performed To analyze pressures in the PEB any extrasystole preceded by at least two sinus beats during the recording of intraventricular pressure was selected A similar analysis with aortic pressure was performed in four cases

The left ventriculograms were performed in the right anterior oblique projection with the use of 0 c c of renografin LVCO was considered when

From the C rdiovascula Su g ry Dep rtment, Cardiol gy and H mo-dynamic Unit La Paz Hosp t l M drid Spain

Rece ed for publ at n N 15 19 8
Accepted fo publication Jan 25, 19 9

Reprint requests Dr José A. S bri o H l rio Eslava 55 M drid 15 Spain.



Fig 1 Left ventriculogram in the right anterior oblique projection *Left panel* diastole *Right panel* systole Note the systolic reduction of the cavity with "sand glass" morphology Mitral valve prolapse is also seen

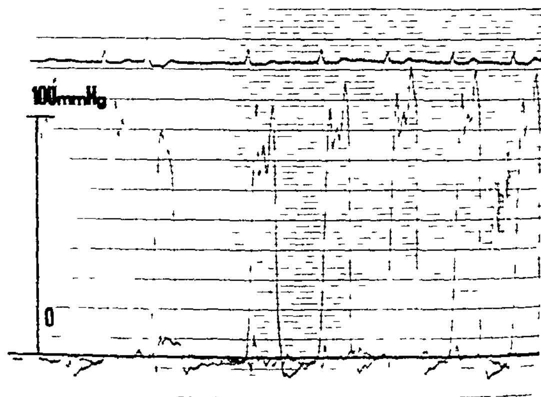


Fig 2 Simultaneous recording of left ventricular and pulmonary wedge pressures. In the postextrasystolic beat (fourth beat) there is a decrease of 10 mm Hg in the left ventricular systolic pressures

apical intracavitary space disappeared during ventricular systole (Fig 1) Ejection fraction circumferential fiber shortening rate and mean normalized systolic ejection rate were calculated from the single plane right anterior oblique projection Coronary arteriography with the Sones technique was performed in eight cases

Results

Clinical features Ten patients (77%) presented with chest pain four (30%) with dyspnea *three* (23%) had palpitations and two (15%) presented with sustained hypertension

Electrocardiograms Nine cases (69%) showed left ventricular hypertrophy two (15%) a pattern

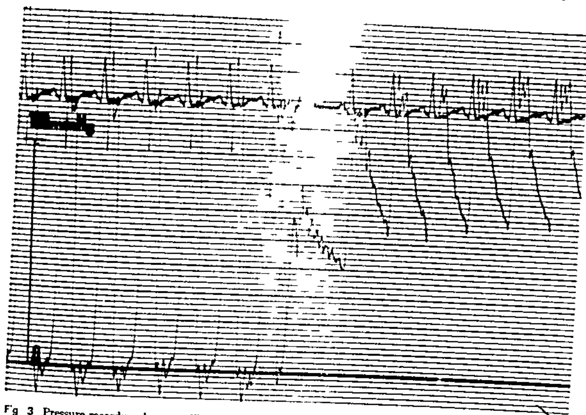


Fig 3 Pressure recording during pullback from left ventricle to aorta The eighth beat is an extrasystolic and corresponds to aortic pressure The following beat (postextrasystolic beat) has an aortic pressure 12.5 mm Hg lower than the subsequent beats Neither transvalvular nor subvalvular aortic gradients are present

Table I Summary of echocardiographic and hemodynamic data

Patient	Age	Echo data			Hemodynamic data					Angiographic data
		LVH	SAM	MP	LVEDP	MV (sec)	MNSER (sec)	EF (%)	Subaortic gradient	
1	36				10	1 99	3 40	ı2	0	
?	37	C	Yes	No	8	2 02	3 33	9?	?0 mm Hg post nitrite	
3	63	No	No	No	8	? 0ɔ	3 60	93	0	
4	16	No	No	Yes	8	3 80	6 33	86	0	
5	50	C	Yes	No	10	5 33	7.23	94	18 mm Hg post nitrite	MP MR
6	43				4	? 88	4 16	91	0	
7	30	A	Yes	No	8	4 54	5 63	92	0	
8	12	A	Yes	No	0	3 09	4 0	8	0	LAD stenosis > 70%
9	45	A	No	No	1?	1 85	3 30	8ɔ	0	MR
10	43				20	2 83	4 62	86	0	MR
11	19	No	Yes	No	10	3 96	6 07	90	0	
1?	13	A	No	Yes	10	5 20	6 00	92	0	
13	30	No	Yes	No	9	5 31	6 63	91	0	MP MR
Mean					9	3 45	5 00	88.53		MR
SD					4 51	1 33	1 39	5 78		MR

Echocardi gram wa not a il bl n Case 1 6 and 10 Coro ry arteriography was n t performed in Cases 4 7 8 1? and 13
Abbreviati ns LVH = l ft e tri lar hype t phy C = conce tric A = asymmetri SAM = syst lic a terior motion of mitral val e l flet MP = m tr l prolapse MR = m t al egurgit tion LVEDP = left ntricular end-diastolic pressure MV_{cf} = m an velocity of circumfer t l fibe sh rtening MNSER = me n n rm lized eject o rate EF = ejection fra t o LAD = left nt rior descending co onary art ry

of intraventricular block and one (7%) showed a pattern of old myocardial infarction

Echocardiograms The recording was available in 10 cases Systolic anterior motion of the anterior leaflet of the mitral valve (SAM) was found in six (60%) asymmetric septal hypertrophy was found[12] in four (40%) symmetric hypertrophy in two (20%) and mitral valve prolapse appeared in two (20%)

Hemodynamic data Only in two cases could a subaortic gradient of 18 and 20 mm Hg be demonstrated after the inhalation of amyl nitrite The left ventricular end diastolic pressure at rest ranged from 0 to 20 mm Hg mean 9 mm Hg A postextrasystolic beat at intraventricular level was recorded in all cases and also at the aortic level in four cases There was a decrease in the systolic pressure peak (from 2 to 25 mm Hg mean 8 5 mm Hg) in every case during the PEB both in the left ventricle and aorta (Figs 2 and 3)

Left ventriculograms Systolic reduction of apical intracavitary space (Fig 1) was noted in all the patients In two cases a mitral valve prolapse was observed and mitral regurgitation was seen in six The ejection fraction ranged from 0 72 to 0 94 (mean 0 89) the circumferential fiber shortening rate between 1 85 and 5 33 (mean 3 45) The mean normalized systolic ejection rate ranged between 30 and 7 23 (mean 5 0)

Coronary arteriography Left dominance was found in three of eight patients studied Obstructive lesions were found in one case

Table I summarizes echocardiographic hemodynamic and angiocardiographic data following an individual display

Discussion

Brockenbrough and associates considered the increase of pressure gradient in the PFB in IHSS as a phenomenon resulting from the obstruction to the left ventricular outflow tract (generated by the increase of contraction in the PEB) In this situation there is a decrease of aortic and suprastenotic ventricular chamber pressures whereas in the substenosis chamber the ventricular pressure increases

There are some common features between IHSS and LVCO without obstruction such as the angiographic left ventricular picture the existence of intraventricular gradient pressure and the echocardiographic SAM Ruzner and coworkers' consider the LVCO as a contraction abnormality that may be seen in a wide spectrum of diseases with left ventricular hypertrophy—for example the IHSS they also believe that LVCO in itself could explain the PEB phenomenon as well as the pressure gradient between obliterated and normocontractile or hypercontractile portions[8] Our cases of LVCO without obstruction presented with a hypercontractile state as may be seen in the contractility indices derived from the left ventriculogram All cases showed a decrease in left ventricular systolic pressure in the PFB a differential feature from IHSS This finding could be attributed to a pressure recording made above an unnoticed obstruction to the left ventricular outflow tract however, several data make this hypothesis unlikely (1) In all cases a pullback from apex to aorta was performed at rest and after nitrite inhalation and only in two cases could a pressure gradient be demonstrated (2) In spite of the evidence that the catheter during the pullback had been placed below the usually obstructing portion in the IHSS in all cases the left ventricular systolic pressure was constant and identical to the aortic pressure during the whole recording (3) Only two of the 10 cases with echocardiograms showed both asymmetric septal hypertrophy and systolic anterior motion of the anterior leaflet of the mitral valve whereas in two cases none of these could be demonstrated

In LVCO without obstruction there may appear artifactual intraventricular pressure gradients due to catheter entrapment in the obliterated portions[14, 16] or true gradients between obliterated and non obliterated portions of the left ventricle[8] Sophisticated catheterization techniques such as left atrial catheterization and pullback from the left ventricle to the left atrial cavity[16] would be needed to adequately demonstrate these facts These maneuvers were not performed in our patients so there is no clear evidence of the behavior of ventricular systolic pressure in the PEB and if the obliterated cavity behaved in the same way as the non obliterated cavity then the decreased pressure was transmitted to the aorta since no left ventricular outflow tract obstruction existed The decrease of the aortic systolic pressure in the PEB is a similar feature both of IHSS and LVCO without obstruction but the decrease of intraventricular pressure in LVCO clearly indicates that different mechanisms are involved i e —obstruction to the left

ventricular outflow tract is the most probable explanation for the decrease in aortic pressure and the increase in intraventricular pressure in IHSS while in LVCO the decrease in aortic pressure is secondary to the decrease in intraventricular pressure

To understand the reasons for the decrease in intraventricular pressure in the PEB in patients with LVCO without obstruction two mechanisms could be invoked (1) The existence of phenomena similar to the ones in IHSS but at a lower level between obliterated and non obliterated portions where gradients could exist and be increased by an augmented contraction (2) Beck and colleagues[17] think that the decrease in intraventricular pressure in the PEB is a common finding in normal hearts and could be explained by the progressive emptiness of the systemic vascular bed during the postextrasystolic pause left ventricular ejection would be performed against low systemic resistances thus resulting in a potentiation of contraction comparatively less than the reduction in the impedance of the systemic vascular bed and therefore resulting in a decrease of the intraventricular pressure However patients with ventricular dysfunction show postextrasystolic potentiation of aortic pressure [1,2] This fact has been explained by the increased aortic impedance in these patients with decreased cardiac output and stroke volume associated with higher peripheral vascular resistances[2]

The cases with obstruction to the left ventricular outflow tract would present with an inverted behavior since the left ventricular ejection fraction would be against a fixed resistance which would result in an increase of the intraventricular pressure In this regard some authors[3] have found in IHSS patients an inverse correlation between the subaortic gradient and the diastolic pressure both in sinus beats and in PEB In patients with LVCO without obstruction the postextrasystolic ventricular pressure would be have as in normal hearts although somewhat increased by the decreased compliance and the decreased diastolic filling

Clinical implications Our data show that the patients with LVCO without obstruction like the patients with IHSS may exhibit a decrease of aortic systolic pressure in the PEB but there is also a decrease of intraventricular pressure This feature would distinguish the cases of LVCO with obstruction from those without obstruction to the left ventricular outflow tract

Summary

Thirteen patients with angiographic left ventricular cavity obliteration are analyzed No transvalvular or subvalvular gradients were present except in two cases with a mild gradient after amyl nitrite inhalation

The commonest clinical features were chest pain (60%) and dyspnea (23%) Electrocardiographically proved left ventricular hypertrophy (70%) was prominent The echocardiograms showed asymmetric septal hypertrophy (40%) symmetric hypertrophy (20%) systolic anterior motion of the anterior leaflet of the mitral valve (60%) and mitral valve prolapse (20%)

In all the patients changes in systolic intraventricular pressure in the post extrasystolic beat were evaluated and a decrease in intraventricular pressure was found in every case In the four cases with extrasystoles recorded in the aorta a similar decrease of aortic pressure was found This behavior is completely different in the hypertrophic cardiomyopathy with obstruction to the left ventricular outflow tract where there is an increase in intraventricular pressure and a decrease in aortic pressure in the postextrasystolic beat

Left ventricular cavity obliteration is an angiographic phenomenon which is common in hypercontractile states being an usual finding in hypertrophic cardiomyopathy In cases without obstruction to the left ventricular outflow tract the decrease in aortic pressure is caused by a different mechanism than the one involved in cases with obstruction In cases without obstruction the decrease in post extrasystolic aortic pressure corresponds to a decrease in intraventricular pressure whereas in subaortic stenosis there is an increase both of intraventricular pressure and gradient with the subsequent decrease in aortic pressure

REFERENCES

1 Hoffman B F Bindler E and Sucking E E Postextrasystolic potentiation of contraction in cardiac muscle Am J Physiol 185 95 1975
2 Braunwald E Lambrew C T, Rockoff S D, Ross J R and Morrow A G Idiopathic hypertrophic subaortic stenosis A description of the disease based upon an analysis of 64 patients Circulation 36(Supp. IV) IV 3 1969
3 Brockenbrough, E C, Braunwald E and Morrow A

G A hemodynamic technic for the detection of hypertrophic subaortic stenosis Circulation 23 189 1961
4 Krasnow N Rolett E Hood W B Jr et al Reversible obstruction of left ventricular outflow tract Am J Cardiol 11 1 1963
5 Martin A M Jr Hackel D B Spach M S Capp M P and Mikat E Cineangiocardiography in hemorrhagic shock AM HEART J 69 283 1965
6 White R I Lewis K B and Criley J M Nonobstructive nature of isoproterenol induced left ventricular pressure gradients in dogs Circulation 32(Supp II) II 219 1965
7 Raizner A Chahine R A Ishimori T, and Awdeh M Clinical correlates of left ventricular cavity obliteration Am J Cardiol 40 303 1977
8 Criley J M Lewis K B White R I and Rose R S Pressure gradients without obstruction A new concept of "Hypertrophic subaortic stenosis Circulation 32 881 1965
9 Greene D G Carlisle R Grant C and Bunnel I L Estimation of left ventricular volume by one plane cineangiography Circulation 35 61 1967
10 Karliner J S Gault J H Eckberg D Mullins C B and Ross J Jr Mean velocity of fiber shortening A simplified measure of left ventricular contractility Circulation 44 323 1971
11 Grossman William Cardiac catheterization and angiography Philadelphia 1974 Lea & Febiger
12 Henry W L Clark C Z and Epstein S E Asymmetric septal hypertrophy (ASH) Echocardiographic identification of the pathognomonic anatomic abnormality of IHSS Circulation 47 225 1973
13 Criley J M Blaufuss A H and Abbasi A S Nonobstructive IHSS Circulation 52 963 1975
14 Adelman A G and Wigle E D Two types of intraventricular pressure difference in the same patient Left ventricular catheter entrapment and right vent outflow tract obstruction Circulation 48 649 19
15 Blundell P E Bedard P Baron R H and W D Nature of intraventricular pressure diff induced by pharmacological agents in dogs, AM J 74 652 1967
16 Morrow A G Vasko J S Henney R P and Br R K Can outflow obstruction be induced wit normal left ventricle? Am J Cardiol 16 540 19
17 Beck W Med M Chesler E and Schrire V I trasystolic ventricular pressure responses, Circ 44 523 1971
18 Wong R Langon R A Cohen J S and Wells Retrograde catheterization of the left atrium in idi ic hypertrophic subaortic stenosis Am J Cardiol 1975
19 Hoffman B F Bartilstone H J Scherlag B Cranefield P F Effects of postextrasystolic po tion in the normal and failing heart Bull N Y Med 41 498 1975
20 Hamby R I Aintablian A Wisoff B G and stein M L Response of the left ventricle in co artery disease to post extrasystolic potentiation C tion 51 428 1975
21 Hamby R I Aintablian A Roberts G and K R J Postextrasystolic aortic pressure pulse resp coronary artery disease AM HEART J 96 195 1
22 Oliver J Azpitarte J Rivero Rey M Cordo and Rabago P Cardiomiopatias hipertroficas va dad de la obstrucción en relación con las modific de la presión diastólica aórtica Rev E p C 31 101 1978
23 Gotsman M S and Lewis B S Left vent volume and compliance in hypertrophic cardio thy Chest 66 498 1974

Myocardial blood flow as a determinant factor in the electrical stability of the myocardium

Michael Cleman M D
P Jacob Varghese M D
Bertram Pitt M D
Baltimore Md

Acute myocardial infarction is followed by a period of electrical instability of the myocardium In experimental animals this electrical instability can be measured by determining the threshold for ventricular fibrillation Previous experiments have shown that ventricular fibrillation threshold (VFT) transiently decreases after acute coronary artery ligation for a period of 5 to 20 minutes in both ischemic and remote nonischemic areas of myocardium The transient decrease in ventric ular fibrillation threshold in remote nonischemic areas of myocardium has raised questions regard ing the mechanisms by which the VFT is lowered following coronary artery occlusion The present study was undertaken to determine the relation ship between regional myocardial blood flow and electrical stability of myocardium as measured by ventricular fibrillation threshold during subendo cardial and transmural ischemia

Materials and methods

Twelve adult mongrel dogs weighing 20 to 35 kilograms were anesthetized with intravenously administered sodium pentobarbital 30 mg /Kg body weight The animals were intubated and ventilated with a Harvard respirator using room air The heart was exposed through a left lateral thorocotomy and suspended in a pericardial cradle Heart rate was kept constant by crushing the sinus node and pacing from the atria with bipolar plunge electrodes at a constant cycle length of 400 msec (150 beats/minute) Systemic arterial pressure was continuously monitored by means of a catheter placed in the central aorta utilizing a Statham P23Db pressure transducer A polyethylene catheter was placed in the left atrium for injection of microspheres A section of the proximal left anterior descending coronary artery was isolated and an electromagnetic flow transducer screw occluder and snare were placed on the artery the flow transducer being more proximal and the snare more distal (Fig 1) Arterial pH was maintained between 7 34 and 7 45 by regulating the respiratory rate and tidal volume settings of the Harvard respirator Arteri al PO was kept above 60 mm Hg with supple mental oxygen and body temperature was main tained between 36 to 38 C with the use of a heating blanket

The fibrillating electrodes were Teflon coated stainless steel diameter 0 01 inch) threaded through a 22 gauge hypodermic needle The terminal portion of this wire was stripped of insulation for 3 mm and made into a hook A pair of such hook electrodes were placed 8 mm apart in the subendocardium and subepicardium of an area supplied by the left anterior descending (LAD) and left circumflex (LCX) coronary arte ries The position of the electrodes was confirmed by recording unipolar and bipolar electrograms from these electrodes and also by localizing the tips of the electrodes by myocardial dissection at the end of the experiments

Ventricular fibrillation threshold determina

F m th Departm t f Med ci e d Pediatrics J h H pk ns Uni rs t School of Med in B ltim re

S pported by th Spect l ed C ter f Rese rch f Isch m c H rt Disease Gr nt P 50 HL 1 6 5 03 w th th N t al I t t tes of H alth nd th Department of Health Ed at n a d Welf re

Rec i ed f publi tio N 1 19 8

Accepted f publ ti Dec 2 19 8

R print reque ts P Ja b V rghese M D C rd Clin Children s Med c l a d S gi al Cent J hn Hopki s Hosp t l 601 N Bro d w y B lt more Md 2120

He ry Stro g De ison Sch l fo 19 6-1977

000 -8 03/80/0303-5 + 06500 60/0 © 1980 The C V M

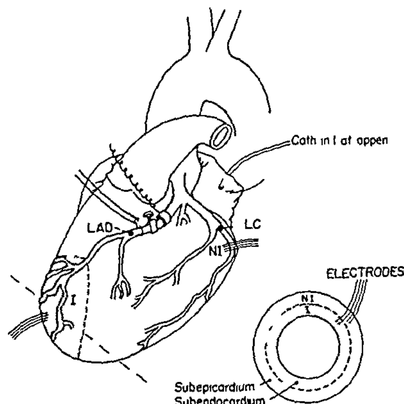


Fig 1 Diagrammatic representation of the experimental model Note the position of the snare screw occluder and flow probe on the left anterior descending coronary artery *(LAD)* *LC* = left circumflex artery *I* = ischemic area *NI* = non ischemic area Position of the electrodes is shown in the cross sectional area

Table I (n = 12)

	LAD ENDO VFT	*LAD ENDO MBF*	*LAD EPI VFT*	*LAD EPI MBF*	*LCX ENDO VFT*	*LCX ENDO MBF*	*LCX EPI VFT*	*LCX EPI MBF*	*LAD ENDO/ EPI*	*LCX ENDO EPI*
Mean	16 1	79 6	15 9	81 0	18.8	79 7	15 5	77 7	.98	1 0
± SD	3 7	15 6	4.3	13 9	6 3	14 2	3 5	10 0	10	0 14

Control values for ventricular fibrillation threshold (VFT) and myocardial blood flow (MBF) in the left anterior descending coronary artery (LAD) region and left circumflex coronary artery (LCX) regions

tion The hook electrodes were connected to a constant current source which delivered a train of 20 pulses each 2 msec in duration and 8 msec apart for a total duration of 200 msec The pulse train was synchronized with Lead II surface electrocardiograms and was programmed to begin 50 msec after the onset of the last paced QRS complex of every twelfth paced beats Following delivery of the pulse train pacing was interrupted for one basic cycle length and then resumed The strength of the pulse train was increased by 1 milliamp (ma) increments until ventricular fibrillation (VF) occurred The least amount of current required to produce VF measured as the voltage drop across a known 1 k resistor was taken as the ventricular fibrillation threshold The heart was then defibrillated with 10 to 20 watt seconds of direct DC current within 10 seconds of VF A 15 minute recovery period was permitted between consecutive VFT determinations VFT determination was repeated until consecutive measurements agreed within 10 per cent of each other

Myocardial blood flow measurements After the control VFT determinations myocardial blood flow (MBF) was measured using the radioactive microsphere technique In this technique 0 05 to 0 15 ml (2 × 10 spheres) of 3M carbonized microspheres ranging in size from 7 to 10 μ and labelled with Sc Nb Ce or Sr were injected through the left atrial catheter and were sampled from the femoral artery at a constant withdrawal speed using a Harvard constant infusion pump At the end of the experiment portions

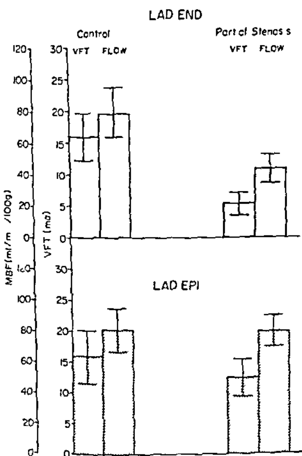


Fig 2 Ventricular fibrillation threshold *(VFT)* and myocardial blood flow *(MBF)* in the endocardium *(END)* and epicardium *(EPI)* of the left anterior descending coronary artery *(LAD)* distribution after partial stenosis of LAD Note with partial stenosis there is a selective decrease in MBF in the LAD subendocardium with an associated fall in VFT No significant change is seen in MBF and VFT in the LAD epicardium

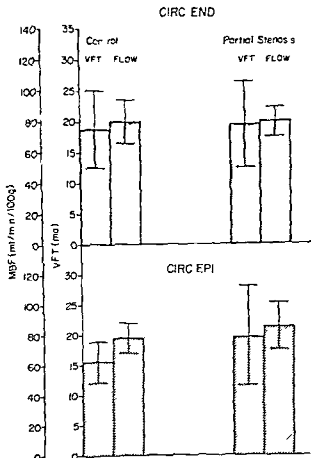


Fig 3 Ventricular fibrillation threshold *(VFT)* and myocardial blood flow *(MBF)* in the endocardium *(END)* and epicardium *(EPI)* of circumflex region following partial stenosis of left anterior descending coronary artery No significant change in MBF or VFT from control values is demonstrated in the circumflex region.

of the myocardium surrounding the electrodes were removed and were sectioned into subendocardium and subepicardium Tissue samples blood blanks and standards were counted for 10 minutes in a scintillation counter Blood flow to the various segments of the myocardium was determined by knowing the withdrawal rate counts in the blood sample and counts in the tissue

Partial stenosis of the left anterior descending artery (LAD) Following determination of control VFT and myocardial blood flow in 12 dogs a 15 second occlusion of the LAD was performed to evaluate the reactive hyperemic response The screw occluder was then tightened until all the hyperemic response was abolished and the resting flow was reduced 25 to 30 per cent from the control values VFT and MBF measurements were repeated after a 15 minute equilibration period

Ligation of the left anterior descending coronary artery (LAD) The LAD artery was ligated in 12 dogs by tying it off with a silk suture proximal to the first diagnoal branch Following a five minute equilibration period VFT was determined and myocardial blood flow was measured by injecting a second set of microspheres

Results

VFT and myocardial blood flow were not significantly different in any of the four regions during the control period (Table I) With partial stenosis myocardial blood flow as determined by the microsphere technique showed a selective decrease of 44 7 per cent ($p < 001$) in the LAD subendocardium accompanied by a decrease of 66 6 per cent ($p < 001$) in VFT values In the LAD subepicardium region there was no signifi-

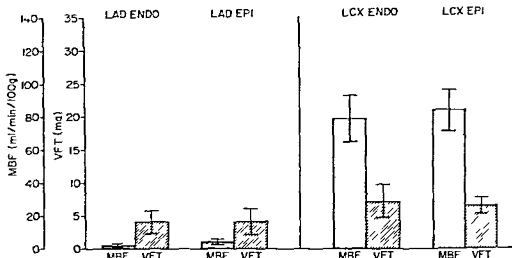


Fig 4 With occlusion of LAD both VFT and MBF fell in the LAD region. There is also a decrease in VFT in the circumflex region without an associated change in MBF

cant changes in myocardial blood flow or VFT (Fig 2) During the partial stenosis of LAD in the circumflex regions myocardial blood flow and VFT values were unchanged from control values (Fig 3)

Following LAD ligation in 12 dogs a decrease in VFT was found in all four regions The LAD subendocardium VFT fell 75 6 per cent from control values which was not significantly different from the decrease found during partial stenosis VFT in the LAD subepicardium also showed a similar decrease with the ligation 74 per cent (p < 0 001) Myocardial blood flow during ligation of LAD decreased in the LAD subendocardium and subepicardium by 98 2 per cent and 91 per cent respectively (Fig 4) In the circumflex subendocardium and subepicardium the myocardial blood flow was not significantly changed following ligation of LAD However the VFTs in the circumflex subendocardium and subepicardium decreased 62 2 per cent and 59 1 per cent respectively (p < 0 001) (Fig 4)

Discussion

The present study has demonstrated three distinct patterns for ventricular fibrillation threshold in relationship to myocardial blood flow

1 With selective subendocardial ischemia produced by partial stenosis of the left anterior descending coronary artery ventricular fibrillation threshold appears to be directly related to myocardial blood flow

2 With ligation of the left anterior descending coronary artery there is a decrease in ventricular fibrillation threshold in both the subendocardial and subepicardial regions of myocardium The decrease in VFT following ligation is associated with a reduction in myocardial blood flow

3 Immediately following left anterior descending coronary artery ligation ventricular fibrillation threshold in remote nonischemic areas of myocardium also shows a significant fall while MBF is unaltered

The finding that VFT is directly related to myocardial blood flow following partial stenosis although not previously reported is not unexpected Partial stenosis as produced in the current experiments results in a selective reduction in subendocardial blood flow Previous studies have shown a decrease in myocardial high energy phosphates following ischemia as well as a loss of intracellular potassium Resting membrane potential shifts toward zero and the fast current is unactivated The slow inward current will still however be active and along with a low resting membrane potential will tend to delay intraventricular conduction The delay in intraventricular conduction predisposes toward reentry which may manifest itself as a ventricular tachycardia or fibrillation The low VFT in this area can thus be explained on the basis of the biochemic and electrophysiological changes that occur with ischemia

A similar relationship between ventricular fibrillation threshold and myocardial blood flow

can be inferred from the studies by Meesmann and colleagues[13] in which it could be shown that ventricular fibrillation threshold following coronary artery occlusion was directly related to collateral blood flow. Other electrophysiological parameters have also been correlated with regional myocardial blood flow. In a recent study, Batsford and associates[1] have shown a direct relationship between effective refractory period of the ischemic myocardium and regional myocardial blood flow. The direct relationship of VFT to myocardial blood flow during subendocardial ischemia lends support to attempts to increase myocardial blood flow either by mechanical or pharmacological means during periods of prolonged ischemia where recurrent ventricular arrhythmias are often a problem.

The lack of correlation between VFT and myocardial blood flow during transmural ischemia is seen in the remote nonischemic areas of myocardium. In the left circumflex regions VFT falls significantly following left anterior descending coronary artery occlusion although flow is unaltered. One possible explanation for the decrease in VFT in remote nonischemic areas of myocardium may be that there is a delay in impulse transmission from the infarcted areas to the normal myocardium resulting in re-entry. Several investigators have shown a marked delay in conduction within an area of experimental infarction. The progressive conduction delay in the subepicardium of the ischemic region often precedes the onset of ventricular tachycardia and ventricular fibrillation. Studies by Bloor and co-workers showing that ventricular fibrillation threshold is related to infarct size might also tend to support this explanation since the larger the infarct the larger the area of conduction delay and hence the greater chance for re-entry and ventricular fibrillation. Although this explanation is attractive, it fails to account for the present finding that VFT is unaltered in remote nonischemic areas of myocardium following partial stenosis and subendocardial ischemia, a situation which would also delay intraventricular conduction and favor re-entry, nor does it account for the finding that VFT in the subepicardial region of the left anterior descending zone was unaffected by subendocardial ischemia in the same zone.

Another possible explanation contributing to the decrease in VFT following transmural ischemia in remote areas of myocardium with unaltered regional MBF may be the release of metabolic factors. For example, catecholeamines have been demonstrated to be released following experimental coronary artery occlusion and increased sympathetic activity has been recorded from preganglionic fibers at the level of the third thoracic vertebrae. Since catecholeamines are known to reduce VFT, it is possible that the reduction in VFT following transmural ischemia in remote areas of myocardium with unaltered regional MBF might be due to this mechanism. Indirect support for this hypothesis comes from studies showing that propranolol may prevent reduction in VFT following experimental coronary artery occlusion. The time course of VFT changes in remote normal areas of myocardium following transmural ischemia does not appear to parallel the time course of catecholamine release in ischemia and suggests other yet unknown metabolic factors for the global electrical instability in transmural ischemia.

Support for yet unknown metabolic factors as the cause of electrical instability in ischemia comes from the study of Downar and associates. In their study, cardiac cells superfused in vitro with coronary venous blood draining an ischemic region developed abnormal electrophysiological properties. These abnormalities were not duplicated if the cells were superfused with coronary venous blood from a normal region, even if the concentrations of potassium, lactate, oxygen, and H were equalized with those of the blood from the ischemic region.

Factors accounting for the tendency toward ventricular fibrillation in ischemia are complex and as yet poorly understood. More effective prevention in therapy of ventricular fibrillation will likely depend upon a better understanding of the interplay of all the major factors—metabolic, hemodynamic, and electrophysiologic. The results of the present experiment would suggest that myocardial blood flow is but one of the major factors to be considered in our search for a better understanding of the mechanism of ventricular fibrillation.

Summary

The role of regional myocardial blood flow on the electrical stability as determined by ventricular fibrillation threshold (VFT) was evaluated in 12 dogs during subendocardial and transmural ischemia. With selective subendocardial ischemia produced by partial stenosis of left anterior

descending coronary artery (LAD) both VFT and myocardial blood flow (MBF) decreased 66 6 per cent ($p < 001$) and 44 7 per cent ($p < 001$) respectively from the control values in the LAD subendocardium VFT and MBF were not significantly different from control values in LAD subepicardium and remote circumflex regions during partial stenosis of LAD

After ligation of LAD VFT in the subepicardium and subendocardium of LAD fell 74 6 per cent ($p < 001$) and 74 per cent ($p < 001$), respectively from control values with an associated decrease in MBF of 98 2 per cent and 91 per cent in each of the regions Following ligation of LAD VFT was also decreased in the circumflex subendocardium and subepicardium 62 2 per cent ($p < 001$) and 59 1 per cent ($p < 001$) respectively from control values while there was no change in MBF from control values in both these regions This study demonstrates the following patterns in electrical instability with ischemia

1 During selective subendocardial ischemia produced by partial stenosis of the LAD, VFT and MBF showed a parallel decline in the LAD subendocardial zone suggesting a direct relationship between these parameters

2 Following LAD ligation with production of transmural ischemia the entire left ventricle became electrically unstable as measured by VFT independent of regional myocardial blood flow This suggests that factors other than MBF significantly influence electrical instability during transmural ischemia

The authors greatly appreciate the technical assistance of Mr Anthony DiPaula and that of Mr Horace Brown and Ms D... Dickson for typing the manuscript

J S Bete J M and Levine H J Distinctive time course of ventricular vulnerability to fibrillation during and after release of coronary ligation Am J Cardiol 34 42 1974

7 Roland J M Dashkoff N Varghese P J and Pitt B Time course of ventricular fibrillation threshold in infarcted and non infarcted myocardium after acute coronary ligation AM HEART J 94 336 1977

8 Braasch W Gudbjarnason S Puri P S Ravens K G and Bing R J Early changes in energy metabolism in the myocardium following acute coronary artery occlusion in anesthetized dogs Circ Res 23 4 9 1968

9 Sobel B E Salient biochemical features in ischemic myocardium Circ Res 35 (Suppl III) 111 1974

10 Jennings R B and Ganote C E Structural changes in myocardium during acute ischemia Circ Res 35 (Suppl III) 111 1974

11 Harris A S Bisteni A Russell R A Brigham J C and Firestone J E Excitatory factors in ventricular tachycardia resulting from myocardial ischemia Potassium as a major excitant Science 119 200 1954

12 Jennings R B Sommers H N Kaltenbach J P and West J J Electrolyte alterations in acute myocardial ischemic injury Circ Res 14 260 1963

13 Cranefield P F Wit A L and Hoffman B F Genesis of cardiac arrhythmias Circulation 47 190 19 3

14 Trautwein W Membrane currents in cardiac muscle fibers Physiol Rev 53 793 1973

15 Meesmann W Gulker H Kramer B and Stephan K Time course of changes in ventricular fibrillation threshold in myocardial infarction Characteristics of acute and slow occlusion with respect to the collateral vessels of the heart Cardiovasc Res 10 466 1976

16 Batsford W P Cannon D S and Zaret B L Relations between ventricular refractoriness and regional myocardial blood flow after acute coronary occlusion Am J Cardiol 41 1083 1978

17 Durrer D Van Dam R T Freud G E and Janse M J Re entry and ventricular arrhythmias in local ischemia and infarction of the intact dog heart Proc K Ned Acad Wet (Biol Med) 74 321 1971

18 Boineau J P and Cox J L Slow ventricular activation in acute myocardial infarction A source of re entrant premature ventricular contraction Circulation 43 0 1973

19 Scherlag B J El Sherif N Hope R and Lazzara R Characterization and localization of ventricular arrhythmias resulting from myocardial ischemia and infarction Circ Res 35 372 19 4

20 Bloor C M Ehsani A White F C and Sobel B F Ventricular fibrillation threshold in acute myocardial infarction and its relation to myocardial infarct size Cardiovasc Res 9 468 1975

21 Gillis R A Role of the nervous system in the arrhythmias produced by coronary occlusion in the cat AM HEART J 81 677 1971

22 Griffiths J, and Leung F The sequential estimation of plasma catecholamines and whole blood histamine in myocardial infarction AM HEART J 82 171 1971

23 Malliani A Schwartz P J and Zanchetti A A sympathetic reflex elicited by experimental coronary occlusion Am J Physiol 217 703 1969

24 Corbalan R Verrier R L and Lown B Differing mechanisms for ventricular vulnerability during coronary artery occlusion and release AM HEART J 92 223 1976

2 Downar E Janse M J and Durrer D The effect of "ischemic" blood on transmembrane potentials of normal porcine ventricular myocardium Circulation 55 4 19 7

Biatrial electrograms during coarse atrial fibrillation and flutter-fibrillation

Carl V Leier M D *
Stephen F Schaal M D **
Columbus Ohio

Atrial flutter was first determined to be a significant dysrhythmia in man by MacWilliam in 1887 It is recognized on the scalar ECG as a rapid (220 to 350 beats per minute) regular undulation of the baseline with identical broad atrial deflections (F waves) The undulation in the inferior limb leads most often resembles a sawtooth pattern Atrial fibrillation is a form of disorganized atrial activation whose scalar ECG features consist of rapid irregular undulation of the baseline with smaller chaotic atrial deflections (f waves) In 1899 Cushney[2] brought atrial fibrillation to the attention of the medical world as an important rhythm disturbance in man

Coarse atrial fibrillation (CAF) and flutter fibrillation (Fl Fib impure flutter) are disorders of atrial activation with scalar ECG features of both atrial fibrillation and atrial flutter The ECG characteristics of CAF are those of fibrillation with superimposed larger but still irregular f waves The scalar ECG of Fl Fib generally shows the superimposition of rapid regular F waves upon a fibrillation baseline or mild variation of the amplitude and/or regularity of a flutter base

Table I Cardiac diagnoses of the study population

	Number of patients
Rheumatic heart disease	12
Primary conduction system disease	9
Hypertensive heart disease	6
Arteriosclerotic heart disease	5
Congenital heart disease	3
Congestive cardiomyopathy	3
Mitral valve prolapse	3
Valvular disease (non rheumatic)	2
Others	4
Unknown	8

1 amyloid heart disease 1 pericardiectomy for calcific pericarditis, 1 Wolff Parkinson White syndrom 1 Lown Ganong Levin syndrome

line While the intracardiac atrial electrograms of atrial flutter and fibrillation have been described little information is available concerning the atrial electrical events of CAF and Fl Fib Irregular high right atrial activity concurrent with regular low right and left atrial activity were noted by Puech and colleagues[3] in a patient with Fl Fib Zipes and DeJoseph reported that three of ten patients with dissimilar atrial rhythms (documented by intracardiac recordings) had simultaneous scalar ECG patterns of Fl Fib or CAF

This study was designed to investigate the electrical events of the atria which occurred during the scalar ECG patterns of CAF and Fl Fib

Methods

Patients The presence of CAF and/or Fl Fib on the scalar ECG was the sole criterion f

From the Division of Cardiology Ohio State University College of Medicine, Columbus, Ohio

Supported by Grants 533 and 631 from the Central Ohio Heart Chapter of the American Heart Association.

Received for publication Dec. 1 19 8

Accepted for publication March 6 1979

Reprint requests Carl V Leier M.D Division of Cardiology Ohio State University Hospitals 653 Means Hall, 466 West Tenth Ave Columbus, Ohio 43?10

* Assistant Professor of Medicine and Pharmacology Division of Cardiology Ohio State University College of Medicine Investigator of the Central Ohio Heart Chapter of the American Heart Association

** Associate Professor of Medicine Division of Cardiology Ohio State University College of Medicine

000?-8 03/80/030331 + 11$01 10/0 © 1980 The C. V. Mosby Co

Table II Atrial electrical activity recorded in the patient population

				No of events	Surface ECG showing	
					CAF	Fl Fib
I	Biatrial fibrillation with periodic regularity			24	24	0
II	Dissimilar interatrial rhythms					
	Right atrium	*Left atrium*				
	Flutter (FF > 160)	Fibrillation		11	0	11
	Flutter (FF ≤ 160)	Fibrillation		4	4	0
	Fibrillation	Flutter (FF > 160)		7	1	6
	Fibrillation	Flutter (FF ≤ 160)		4	3	1
	Flutter (FF > 160)	Quiescence		2	0	2
	Flutter (FF ≤ 160)	Quiescence		1	1	0
	Fibrillation–reg	Quiescence		1	1	0
	Atrial tachycardia	Flutter		1	0	1
III	Dissimilar right intra atrial rhythms					
	High right	*Low right*	*Left atrium*			
	Flutter (FF > 160)	Fibrillation	Fibrillation	2	2	0
	Fibrillation	Flutter (FF > 160)	Fibrillation	1	0	1
	Fibrillation	Flutter (FF ≤ 160)	Fibrillation	1	1	0
	Fibrillation	Flutter (FF > 160)	Flutter	2	0	2
	Flutter (FF > 160)	Fibrillation	Flutter	1	0	1
	Atrial tachycardia	Flutter	*	1	0	1
	Atrial tachycardia	Fibrillation	*	1	0	1
IV	Dissimilar atrial flutter rates					
	Interatrial (right ≠ left)			4	1†	3
	Right intra atrial (high right ≠ low right)			3	0	3
V	Fast flutter–biatrial					
	FF = 150-170 msec			12	0	12
	FF < 150 msec			4	3†	1
VI	Fragmented F deflection					
	FF > 160 msec			5	0	5
	FF ≤ 160 msec			4	2‡	2

*Rhythms of high right and low right atrium were the same
†One patient demonstrated both features CAF and Fl Fib
‡Both patients showed features of CAF and Fl Fib

inclusion in the study CAF was defined as fibrillation (fine undulation) of the scalar ECG base line with superimposed larger f waves (≥ 1 mm)[5] of unequal amplitude and unequal f f intervals ECG recordings showing a fibrillation baseline with varying periods of rapid regular waves of uniform amplitude were designated Fl Fib These dysrhythmias either occurred spontaneously or were induced by rapid atrial pacing of atrial flutter paroxysmal atrial tachycardia or sinus rhythm

Fifty seven patien were tudied The mean age of the patient popula n a years (range 21 to 81) with 25 fen m ales Various cardiac disease state e d (Table I) and the diagnoses were ith car diac catheterization in Thirty eight (67%) of the patier ographic cardiomegaly 27 (47%) had clinical and/or radiologic evidence of congestive heart failure and six had moderate to severe chronic obstructive pulmonary disease Right and/or left atrial enlargement was noted on cardiac fluoroscopy and/or the echocardiogram in 32 (56%) patients Atrial conduction studies[4] were performed in 19 patients within one year of this study and 18 were found to have atrial conduction disease Thirty patients were receiving a cardioactive drug at the time of study (20 patients on digitalis five on quinidine sulfate two on propranolol and three on propranolol and quinidine sulfate) All patients were clinically euthyroid two of the patients were taking a thyroid preparation

Atrial recording studies Written informed consent was obtained from each patient prior to each study No premedication was administered In 56

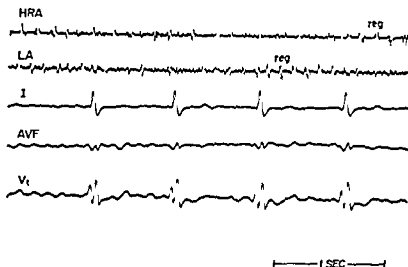


Fig 1 Electrograms from the high right atrium *(HRA)* and left atrium *(LA)* showing fibrillation with periodic slowing and regularity *(reg)* A similar pattern was present in the low right atrial region Coarse atrial fibrillation was present in aVF and V1

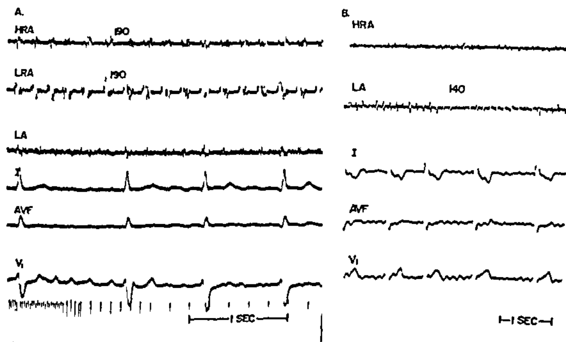


Fig 2 Biatrial electrograms during dissimilar atrial rhythms in two patients *A* High right *(HRA)* and low right *(LRA)* atrial recordings showing flutter (FF = 190 msec) and left atrial recording *(LA)* showing fibrillation while impure flutter and flutter fibrillation were noted on the scalar ECG (50 mm /sec paper speed) *B* Surface ECG of coarse atrial fibrillation with high right atrial *(HRA)* fibrillation and left atrial *(LA)* fast flutter (FF = 140 msec) Separate low right atrial recordings also showed fibrillation (75 mm /sec paper speed)

patients right and left atrial electrograms were recorded from bipolar electrode (interpole distance of 1 cm) catheters placed respectively within the right atrium and esophagus (posterior to the left atrium) and/or coronary sinus A minimum of two catheters were placed in the right atrium one for recording the high right atrial electrogram and the other for recording the low right atrial electrogram Left atrial electrograms were not recorded in one patient In 36

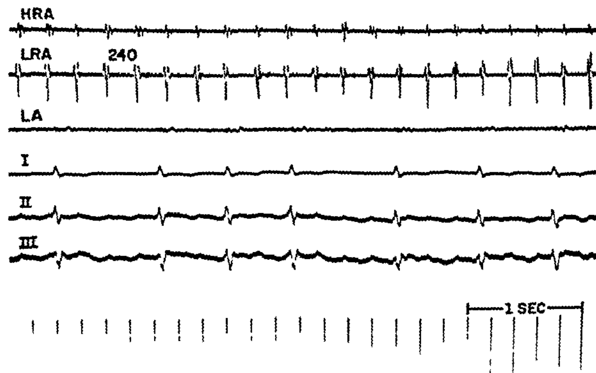


Fig 3 Right atrial flutter (*HRA* and *LRA* FF = 240 msec) and left atrial (*LA*) quiescence with impure flutter and flutter fibrillation pattern present on the scalar ECG

patients a six pole catheter was also placed across the tricuspid valve for the simultaneous recording of low right atrial bundle of His and the ventricular depolarizations High right atrial (HRA) low right atrial (LRA) and left atrial (LA) electrograms and three scalar ECG leads (usually I aVF and V1) were recorded simultaneously on an Electronics for Medicine DR 12 recorder at paper speeds of 25 50 and 100 mm/sec Intracardiac and esophageal electrode signals were amplified in a frequency range of 30 to 500 Hz Atrial pacing was performed with a Grass Instrument S88 stimulator and isolation unit

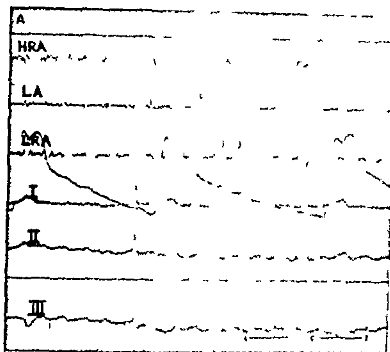
An atrial electrogram showing an *irregular* depolarization pattern (at atrial rates > 360/minute) was defined as fibrillation a *regular* depolarization pattern at atrial rates in the range of 220 to 400/minute was defined as flutter

Results

The electrical [illegible] atrium occurring during CAF and Fl Fib [illegible] population are presented in Table II

Fibrillation with periodic regularity Twenty four of the patients had [illegible] grams showing biatrial fibrillation [illegible] showing and regularity (Fig 1) and the scalar ECG of each of these patients revealed CAF

Dissimilar atrial rhythms Transient (> 1 and < 5 minute duration) or persistent (> 5 minute duration) dissimilar right and left atrial rhythms were observed in 31 patients Flutter of one atrium and fibrillation of the other was the most common form of dissimilar atrial rhythms noted (Fig 2 *A* and *B*) When the electrograms demonstrated flutter of one atrium and fibrillation of the other atrium the scalar ECG showed CAF in seven of eight patients whose flutter FF interval was ≤ 160 msec and showed Fl Fib in 17 of 18 patients with FF intervals > 160 msec Four patients demonstrated dissimilar atrial rhythms with left atrial quiescence Two of these patients had right atrial flutter at FF intervals of 240 and 250 msec with low amplitude flutter and Fl Fib on the scalar ECG (Fig 3) another patient had rapid right atrial flutter (FF = 160 msec) with the scalar ECG of CAF the last patient had right atrial fibrillation (with periodic regularity) with fibrillation and infrequent coarseness on the scalar ECG A patient previously reported had scalar ECG patterns of Fl Fib and impure flutter during right atrial tachycardia and left atrial



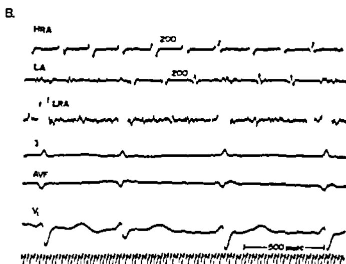


Fig 4 Dissimilar right intra atrial rhythms A High right atrium *(HRA)* shows fibrillation while the low right *(LRA)* and left atrium *(LA)* demonstrate flutter with an FF interval of 180 msec Flutter fibrillation was noted on the surface ECG B Another patient with low right atrial *(LRA)* fibrillation occurring simultaneously with high right atrial *(HRA)* and left atrial *(LA)* flutter (FF = 200 msec)

flutter and Fl Fib and CAF during periods of interatrial Wenckebach

Dissimilar right intra atrial rhythms Dissimilar rhythms within the right atrium itself were observed in nine patients Seven instances involved flutter of either the high or low right atrium and fibrillation of the remaining portion of the right atrium (Fig 4) The simultaneous left atrial recording showed either flutter or fibrillation and again the scalar ECG demonstrated Fl Fib if the FF interval exceeded 160 msec and CAF if the FF ≤ 160 msec A patient with high right atrial tachycardia (AA = 440 msec) had transient episodes of low right atrial flutter (FF = 220 msec) interchanging with periods of low right atrial fibrillation (Fig 5) No left atrial recordings were obtained on this patient and the scalar ECG showed Fl Fib

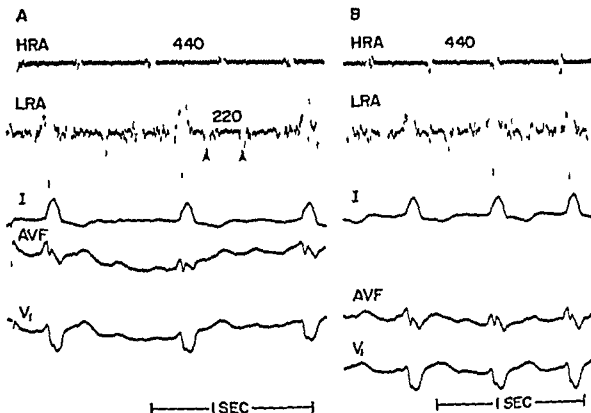


Fig 5 Two different forms of dissimilar right intra atrial rhythms in the same patient *A* High right atrial recording *(HRA)* showing a regular atrial tachycardia with an AA of 440 msec A simultaneous low right atrial recording *(LRA)* demonstrates a regular faster atrial tachysystole (flutter FF = 220 msec) Flutter fibrillation and impure flutter pattern are present on the scalar ECG Placement of a premature atrial depolarization (extrastimulus) in the low right atrial region changed the LRA to fibrillation as noted in *panel B* The HRA remained in regular tachycardia at AA = 440/minute Left atrial recordings are not available

Table III Atrial electrical events noted during the scalar ECG recordings of coarse atrial fibrillation ($n = 39$)

Atrial electrical events		No	%
Biatrial fibrillation with periodic regularity		24	6
Dissimilar atrial rhythms		10	2
FF > 160 msec			
RA Fib LA Fl	1		
FF ≤ 160 msec			
RA Fl LA Fib	4		
RA Fib LA Fl	3		
RA Fl LA-quiet	1		
RA Fib LA-quiet	1		
Dissimilar right intra atrial rhythm		3	8
FF > 160 msec			
HRA Fl LRA Fib LA Fib	2		
FF ≤ 160 msec			
HRA Fl LRA Fib LA Fib	1		
Fast flutter biatrial		2	5
FF > 160 msec	0		
FF < 160 msec	2		

Abbreviations FF = flutter FF [illegible] Fib = fibrillation Fl = flutter HRA = high right atrium LA = left atrium LRA = low right atrium [illegible] AT = atrial tachycardia quiet = quiescent RA = right atrium (high and low)

Dissimilar atrial flutter rates Transient unequal flutter rates of each atrium occurred in four patients Three of these patients had scalar ECG recordings of Fl Fib with right/left atrial FF intervals of 200/270 155/170 and 230/170 msec (Fig 6) Features of both CAF and Fl Fib were observed on the scalar ECG tracing of a patient with a right flutter interval of FF = 190 msec and left atrial flutter interval of 170 msec A patient with Fl Fib had transient episodes of dissimilar flutter rates within the right atrium itself this patient had flutter (FF = 240 msec) of the left and low right atrium with a slower somewhat irregular high right atrial rhythm secondary to right intra atrial and interatrial Wenckebach (Fig 7) Another patient had two different episodes of Fl Fib with unequal flutter rates within the right atrium itself the left and high right atrial flutter was faster than the low right atrial flutter on one occasion with FF intervals of 180 and 200 msec respectively and the other episode consisted of left atrial fibrillation high right atrial flutter with an FF interval of 200 msec and low right atrial flutter with an FF interval of 230 msec (Fig 8)

Fast and fragmented flutter The remainder of the patients with CAF or Fl Fib had either biatrial rapid (FF $\leq$ 170 msec) flutter and/or fragmented (duration of F deflection $\geq$ 80 msec) flutter (Fig 9) In biatrial rapid flutter alone FF intervals $\geq$ 150 msec were usually manifested as Fl Fib on scalar ECG and FF intervals $<$ 150 msec as CAF or CAF with episodic Fl Fib

Discussion

This study shows that the scalar electrocardiographic manifestations of CAF and Fl Fib may be secondary to a variety of atrial electrical events Tables III and IV summarize the atrial electrical events recorded during these dysrhythmias Transient or persistent CAF occurred 39 times and Fl Fib 53 times in this study population

Coarse atrial fibrillation (Table III) The majority (62%) of CAF events were secondary to biatrial fibrillation with periodic slowing and regularization In contrast to the regular frequency of flutter the regularization of fibrillation showed f f intervals which were still somewhat variable and usually quite short at $<$ 140 msec (atrial rate $>$ 430/minute) The periods of regularization noted on the atrial recordings did not always

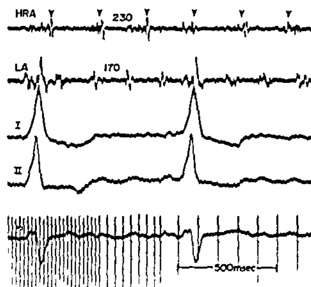


Fig 6 Transient unequal interatrial flutter rates recorded simultaneously with a flutter fibrillation pattern on the surface ECG A lower fragmented flutter (FF = 230 msec *arrows* indicate measurement points of F deflections) occurred in the high right atrium *(HRA)* simultaneous with a faster left atrial *(LA)* flutter (FF = 170 msec) A very mild variation of the HRA FF interval is present A separate recording from the low right atrium showed the same flutter rate as the HRA

coincide with the periods of coarseness on the scalar ECG this indicates that areas of the atria (e g anterior RA lateral LA etc) not directly recorded by the three electrodes contributed significantly to the depolarization pattern of the atria and thereby modified the scalar ECG recordings CAF was also associated with electrograms showing dissimilar right and left atrial rhythms dissimilar right intra atrial rhythms and fast flutter Most of the patients (nine of 10) with CAF and dissimilar atrial rhythms had flutter rates $\geq$ 375/minute (FF $\leq$ 160 msec) Two patients with FF intervals $>$ 160 msec and the scalar ECG of CAF had dissimilar intra atrial rhythms with flutter only in the high right atrium and fibrillation in the low right and left atrium Fragmentation of the F waves on the atrial electrograms was generally not found to be a cause of CAF although two patients with rapid fragmented F waves (FF intervals $<$ 160 msec) had scalar features of both dysrhythmias (CAF/Fl Fib Table II) Rapid biatrial flutter alone (without dissimilar rhythms or fragmentation) was found during CAF when the flutter rate exceeded 400/minute (FF $<$ 150 msec) the pre



Fig 7 Atrial electrograms showing regular left and low right atrial *(LA LRA)* flutter (FF = 240 msec) with Wenckebach periodicity occurring in the high right atrial region *(HRA)* The time interval (msec) between the LA and HRA deflections are indicated above the HRA recording X = dropped HRA beat A separate recording at 25 mm /sec. paper speed and at a slower ventricular rate showed Fl Fib and impure flutter pattern on the scalar ECG

Table IV Atrial electrical events observed during the scalar ECG recordings of flutter fibrillation (n = 53)

Atrial electrical events		*No*	%
Dissimilar atrial rhythms		21	40
FF > 160 msec			
RA Fl LA Fib	11		
RA Fib LA Fl	6		
RA Fl LA-quiet	2		
RA PAT LA Fl	1		
FF ≤ 160 msec			
RA Fib LA Fl	1		
Dissimilar right intra atrial rhythm		6	11
FF > 160 msec			
HRA Fl, LRA Fib LA Fl	1		
HRA Fib LRA Fl, LA Fl	2		
HRA Fib LRA Fl LA Fib	1		
HRA PAT LRA Fl, LA ?	1		
HRA PAT LRA Fib LA	1		
Dissimilar atrial flutter rates		6	11
Interatrial	3		
Right intra atrial	3		
Fast flutter–biatrial		13	25
FF = 150-170 msec	12		
FF < 150 msec	1		
Fragmented F deflection		7	13
FF > 160 msec	5		
FF ≤ 160 msec	2		

Abbreviations see Table III

sence of small areas of fibrillation in locations not directly recorded by the electrodes cannot be excluded in these patients

Flutter fibrillation (Table IV) In contrast to CAF Fl Fib was never present on the scalar ECG when the electrograms demonstrated biatrial fibrillation with periodic regularity Sixty two per cent of the Fl Fib events were associated with dissimilar right and left atrial rhythms dissimilar right intra atrial rhythms or dissimilar flutter rates The remainder of the Fl Fib events were secondary to rapid flutter (FF ≤ 170) or fragmentation of the F waves It appears that regular activity must be present in at least one portion of the atria in order to have Fl Fib represented on the scalar ECG The remaining portions of the atria may demonstrate fibrillation atrial tachycardia a different flutter rate electrical quiescence or a combination of these In instances of biatrial flutter the flutter must be rapid (FF = 150 to 170 msec) or fragmented to produce a Fl Fib appearance Ninety two per cent (37 of 40) of patients with scalar Fl Fib tracings and atrial electrograms showing dissimilar rhythms or rates or fragmentation had flutter FF intervals ≥ 160 msec and 92% (12 of 13) of patients with Fl Fib and atrial recordings of biatrial flutter (same rates and without fragmentation) had FF intervals ≥ 150 msec In general a FF interval above 160 msec tends to produce the scalar ECG tracing of Fl Fib and an interval below 150 msec will usually show CAF on ECG In the FF interval range of 150 to 160 msec the scalar ECG pattern will depend on the atrial electrical activity occurring at the time (pure biatrial flutter = Fl Fib dissimilar rhythms or rates or fragmentation = CAF or CAF/Fl Fib)

The incidence of dissimilar right and left atrial rhythms was high in our study population occurring in 40% of the Fl Fib recordings Dissimilar right intra atrial rhythms probably belong to the dissimilar atrial rhythm family and differ only in that the boundary of the dissimilar rhythms is located between the two right atrial electrodes instead of between the right and left atrial recording electrodes In most instances the atrial catheters were repositioned to look for variations in the atrial electrogram or to identify boundaries of flutter or fibrillation Intermediate areas were frequently identified which showed regularity with intermittent fragmentation or irregularity and were bounded by relatively pure flutter on one border and fibrillation on another Overdrive

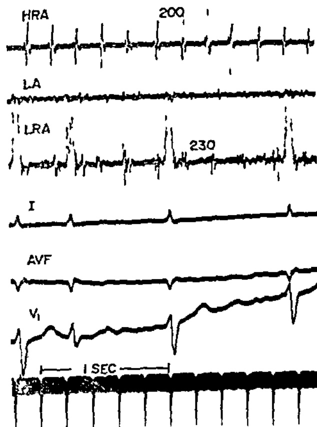


Fig 8 Transient unequal right intra atrial flutter rates in a patient with dissimilar atrial rhythms and flutter fibrillation on the surface ECG (Lead V_1) The right atrium *(HRA* and *LRA)* was in flutter and the left atrium *(LA)* was in fibrillation The high right atrium flutter rate was 300/minute (FF = 200 msec) while that of the low right atrium was 260/minute (FF = 230 msec) The FF intervals of the slower flutter *(LRA)* were slightly irregular (≤ 10 msec variation)

pacing applied to the region of flutter (while the remainder of the atria was in fibrillation) consistently converted the flutter region to fibrillation While these observations suggest that the dissimilar atrial rhythms of flutter and fibrillation are not independent this study does not indicate which of the two dysrhythmias is dominant The flutter zone may be dominant and rapid pacing of this region may move the disorganization of conduction (fibrillation zone) closer to the recording catheter The studies of Zipes and DeJoseph suggest that the fibrillation regions are dominant and that the rhythm and rate of the flutter zone are controlled by a longer and more uniform refractory period During overdrive pacing the refractory period of the flutter zone shortens and/or becomes non uniform allowing more of

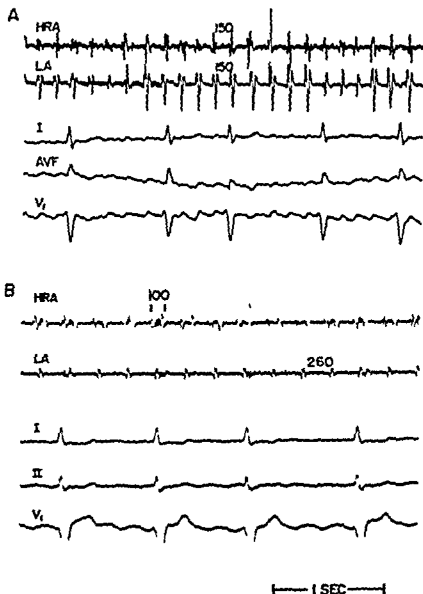


Fig 9 *A* Biatrial recordings of fast flutter (FF = 150 msec) manifested on the scalar ECG as flutter fibrillation *B* The right atrial F deflection is fragmented to a duration of 100 msec during a flutter rate of 230/minute (FF = 260 msec) The simultaneous surface ECG showed flutter fibrillation and impure flutter

the fibrillatory impulses to enter the region Overdrive pacing of right atrial flutter during left atrial quiescence did not alter the flutter rhythm and rate or converted the region into fibrillation Although the electrical quiescence was explored with multiple catheter locations (full length esophageal and coronary sinus readings) at high gain and various recording frequencies it is possible that very fine fibrillation was present in or around the quiescent region

The mechanism of different intra- or interatrial flutter rates (dissimilar atrial flutter rates) is not clear The region with a lower flutter rate probably has a longer refractory period and is dependent upon conduction from the faster flutter region for its impulses The activation of a passive region with a longer refractory period to the more rapid regular impulses of another region would be slightly irregular as noted in Figs 6 and 8 or would show a set conduction pattern as observed in the patient with interatrial and right intra atrial Wenckebach (Fig 7) and in another patient with interatrial Wenckebach and 2 1 interatrial conduction[4] The dissimilar atrial flutter rate events were all transient (≤ 5 minutes duration) implying that this rhythm disturbance is unstable and will probably not persist as a chronic atrial dysrhythmia

Most patients in this series had cardiac disease with cardiomegaly alone (20%) or cardiomegaly with clinical and/or roentgenographic congestive heart failure (47%) Fluoroscopic and/or echocardiographic data revealed that atrial enlargement was present in 56% of the patients Twenty five of 29 (86%) patients who spontaneously developed CAF or Fl Fib had cardiomegaly and/or atrial enlargement and/or evidence of congestive heart failure Thus only four of 29 patients (14%) with spontaneous CAF or Fl Fib did not have cardiomegaly atrial enlargement or congestive failure Two of these remaining four patients underwent atrial conduction time measurements both demonstrated prolonged atrial conduction times indicative of atrial conduction disease Therefore of 29 patients who had developed spontaneous Fl Fib or CAF a cardiac pathophysiologic etiology was not identified in only two patients The patient prototype for CAF and Fl Fib in our study was an individual with a form of cardiac disease accompanied by one or more of the following (1) cardiomegaly (2) atrial enlargement (3) congestive heart failure or (4) atrial conduction disease

This study does not provide direct information on the mechanisms of atrial fibrillation or flutter but it does illustrate some of the interactions of the two dysrhythmias The scalar ECG recordings of the relatively common dysrhythmias CAF and Fl Fib appear to be secondary to an interesting spectrum of atrial electrical events

Summary

Right and left atrial electrograms were recorded in 57 patients who demonstrated coarse atrial fibrillation or flutter fibrillation on the scalar electrocardiogram Atrial electrograms in coarse atrial fibrillation most often showed biatrial fibrillation with periodic slowing and regularity while dissimilar interatrial or right intra atrial rhythms were noted less frequently Flutter fibrillation on the scalar ECG required the presence of rapid regular tachysystole (flutter) somewhere in the atria and was usually associated with dissimilar interatrial or right intra atrial rhythms dissimilar atrial flutter rates or fast or fragmented flutter Coarse atrial fibrillation and flutter fibrillation may be secondary to a variety of atrial electrical events

The authors would like to thank Mrs Marlene Griffin Ms Ladd Snyder Ms Max Bacher Mrs Margaret Chambers and Mr Fred Davis for their technical assistance

REFERENCES

1 MacWilliam J A Fibrillary contraction of the heart J Physiol 8 296 1887
2 Cushney A R On the interpretation of pulse tracings J Exp Med 4 327 1899
3 Puech P, Latour H and Grolleau R Le flutter et ses limites Arch Mal Coeur 61 116 1970
4 Zipes, D P and DeJoseph R L Dissimilar atrial rhythms in man and dogs Am J Cardiol 32 618 1973
5 Peter R H Morris J J, and McIntosh H D Relationship of fibrillatory waves and P waves in the electrocardiogram Circulation 33 599 1966
6 Leier C V Meacham J A and Schaal S F Prolonged atrial conduction—a major predisposing factor in the development of atrial flutter Circulation 57 213 1978
7 Scherlag B J Lau S H Helfant R H Berkowitz W D Stein E and Damato A N Catheter technique for recording His bundle activity in man Circulation 39 13 1969
8 Leier C V and Schaal S F Dissimilar atrial rhythms—a patient with interatrial block Br Heart J 39 680 1977

Extension of experimental infarction with nicotine and estimates of infarct size

Ronald R Masden M D
Nancy C Flowers M D
Louisville Ky

There has been a great deal of interest in both the public and the scientific quarter in the past three decades in the possible role that certain constituents of tobacco smoke play in the development of coronary atherosclerotic heart disease (CAHD) and its sequel myocardial infarction and in the occurrence of sudden death[1] This study is focused upon one constituent of tobacco smoke nicotine and is designed to address the question whether or not the acute administration of nicotine after infarction alters infarct size

A secondary purpose of this study was to further test in a larger group of animals with an intervention an electrical infarct sizing technique previously reported

Methods

Nineteen dogs selected to weigh between 20 and 30 kilograms were anesthetized with sodium pentobarbital intravenously administered 30 mg per kg Controlled respiration was established with a Harvard pump respirator utilizing room air Tidal volumes were calculated to consider the size of the animal and the dead space of the instrumentation Prior to any intervention normal arterial blood gas values were verified

From 142 surface sites potentials were recorded on analog magnetic tape which was subjected to analog to digital conversion and digitized at a sampling rate of 1 000 per second For digitizing for averaging 100 cycles and for time alignment of the averaged data the fiducial mark was obtained from a shaped and filtered simultaneous control Lead II The effective frequency response of the entire system was between 0 2 and 3 000 Hertz Onset of activation was specified with the help of a PDP 9 computer search of the 142 leads in which the first of eight successive increases in the root mean square value of the total surface electrocardiogram is programmatically determined The information is then displayed in isometric projection map form at 1 msec intervals throughout the period of ventricular excitation Such data were obtained and recorded both prior to and one week after closed chest myocardial infarction A point by point subtraction of the chest voltages recorded after infarction from those recorded before was performed msec by msec from each recording site (Fig 1) The root mean square value of the difference map was compared at each msec and represented the electrical estimate of infarct size This estimate of size was compared with the anatomic estimate of infarct size described below

The technique of infarction utilized a Sones No 7 or 7½ catheter advanced under fluoroscopic control via the right carotid artery and positioned well into the left main coronary artery at the bifurcation of the circumflex and the left anterior descending branch After a left coronary arteriogram was performed a 0 025 inch catheter guide wire was passed and positioned in the left anterior

From the Division of Cardiology Department of Medicine University of Louisville School of Medicine

This investigation was supported … Kentucky Tobacco and Health Research … grants HL 19779 and … Institutes of Health … by the Veterans Administration

Received for publication …

Accepted for publication …

Reprint requests … Chief Division of Cardiology … Louisville School of Medicine … KY 40202

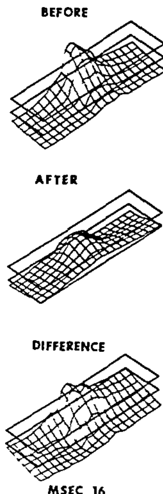


Fig 1 High frequency recordings of surface potential have been obtained at each grid intersection of the body surface maps Left extremes of the map represent the center of the back the eleventh vertical grid line from the left represents the midsternal line The superior map border is at a level just below the clavicle while the inferior map border is at the level of the umbilicus The animal s thorax is portrayed as a 30 degree isometric projection map in order that positive voltage expressions appear as peaks and negative ones as sinks A point by point subtraction of the map recorded after myocardial infarction from the map recorded before myocardial infarction is carried out at each grid intersection at 1 msec intervals throu hout the QRS complex A difference map is thus calculated at each msec interval and its volume is determined Such volumes representati e of infarcted muscle are correlated with the actual anatomic volume at each msec (See text)

descending branch distal to the origin of the first diagonal (Fig 2) The catheter was removed and a sterilized metal bead was placed over the guide The catheter was then again inserted over the guide and the bead was advanced to the proper position in the left anterior descending branch

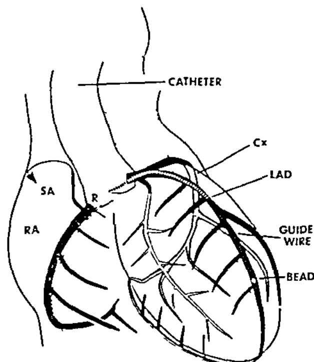


Fig 2 The technique of myocardial infarction utilizing a completely closed-chest preparation is demonstrated Through an arteriotomy in the right carotid artery a coronary arteriogram is performed with an end hole catheter The guidewire is inserted through the catheter into the approxi mate location for bead placement The catheter is removed a metallic bead is placed over the guide the catheter is replaced and the bead is expelled off the end of the guide at the desired location

After placement the location of the bead was further verified with a follow up coronary arterio gram Constant recording of multiple lead surface voltages allowed immediate confirmation of the current of injury

The catheter instilled bead technique of producing a controlled size myocardial infarction was developed over the course of five years A stable survival rate of 76% was achieved Our ability to control infarct size was tested in ten animals divided into two groups The first group was sequentially infarcted in one set of experi ments and compared with the second set who were infarcted 10 months later utilizing the identical technique but in a different laboratory setting entirely Paired t and Student s t tests revealed no differences in the infarct size (deter mined morphologically as described below) reas suring us that we had achieved a technique that was reproducible Animal weight predicts heart

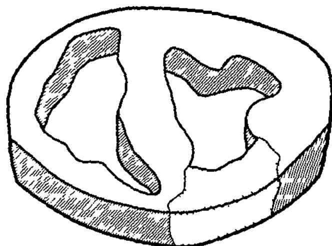


Fig 3 A diagrammatic representation of the method of preparing the hearts in 1 cm slices for staining and planimetry or photography followed by planimetry The planimeterized area of infarction was obtained for each 1 cm slice and its percentage of the total myocardium was calculated (See text)

size in normal dog quite well Thus by continuing care in selection of animal size very homogenous groups resulted which were comprised of dogs whose weights and heart masses were not significantly different at the outset

An infusion of nicotine in the amount of 800 μg/minute was initiated after a stable electrical state had been reached following bead placement The infusion was continued for a 15 minute period after which the animals were observed until electrical stability was again achieved The dogs were then returned to the animal care facility to recover from anesthesia

One week after infarction a second total body surface map was recorded following which the dogs were rapidly killed The intact hearts were removed and in the first six animals the hearts were immediately frozen with liquid nitrogen then sliced and prepared for histochemical staining Each measured centimeter slice of myocardium was subsectioned for microscopic study using 40 micron thick sections Stains were applied for hematoxylin and eosin as well as periodic acid Schiff staining and special histochemical stains for lactic and succinic dehydrogenase From these six dogs heart preparations it was ascertained that at one week the extent of the infarcted zone could be clearly determined for reproducible planimetry without the necessity of special enzyme staining Precise 1 cm thick slices of the myocardium were photographed and traced onto ruled paper so that the total surface area for each slice could be determined The planimeterized area of the myocardial infarction was obtained for each slice and its percentage of the volume of the total myocardium was calculated from the area estimates by Newton s method[10] (Fig 3) The percentage of infarction then was calculated and expressed as the percentage of the total heart volume rather than the left ventricular volume alone

Infarction size could then be expressed in terms of the amount estimated electrically, and the amount determined by direct morphologic assay Further the degree of correspondence of the two methods of sizing was established by determining the correlation between the anatomically determined infarct volume and each instantaneous estimate of the electrical loss

Results

After initiation of nicotine there was an increase in sinus node discharge up to 40% of the baseline rate for a period of about five minutes During this same period single ventricular premature beats salvos and short bursts of ventricular tachycardia occurred During the last 10 minutes of exposure the animals exhibited relative electrical stability with total cessation of sequential ventricular premature beats and either a complete absence of ectopic activity or only rare single ventricular premature beats At the time of return to the animal facility some 90 minutes post infarction the two groups were indistinguishable in terms of rhythm and conduction

In order to apply a paired t test to groups of the same size to compare the sizes of the infarctions in terms of percentage of heart volume we eliminated one of the 10 dogs not having received nicotine In order not to prejudice the comparison in favor of the hypothesis that nicotine given acutely increases infarct size we excluded from consideration for the paired t test only the dog from the group not exposed to nicotine with the smallest percentage of infarcted myocardium Total heart volumes ranged from 69 41 to 122 3 cubic centimeters with no difference between groups Infarctions ranged from 99 cubic centimeters (which was in the non infarct group and not included in the paired t test) to 13 4 cubic centimeters

The volume of infarcted myocardium expressed as percentage of total heart volume was deter

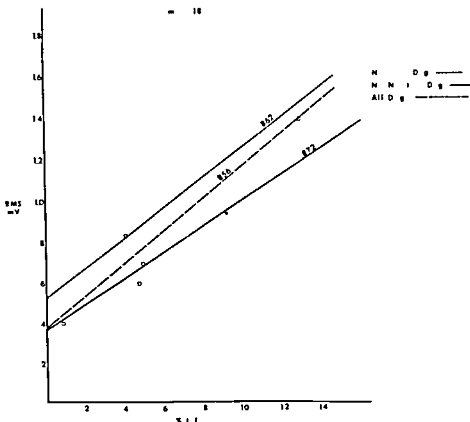


Fig 4 At msec 18 the root mean square (RMS) in mV of the infarct map is compared with the morphologically determined size of infarction Regression lines demonstrating the level of correlation between the electrically determined infarct volume and the morphologically determined infarct volume for three groups of animals are shown The first regression line *(dashed line)* demonstrates the correlation coefficient of the total group of animals, *the dotted line* represents the correlation coefficient for the animals subjected to nicotine and *the solid line* represents the animals not exposed to nicotine Note the hi h degree of correspondence between the electrical and the morphologic infarct volumes Maximum correlation in each animal occurred during the middle of ventricular activation at 17 or 18 msec

mined to be greater in the nine animals of the nicotine group compared to the nine animals not exposed to nicotine who had the largest infarctions ($p < 0.0001$)

In Fig 4 we see regression lines demonstrating the level of correlation between the electrical and morphologic zones of infarction in all 19 dogs (dashed lines) in the dogs exposed to nicotine (dotted lines) and in the dogs not exposed to nicotine (solid line)

In Fig 5 we see the results of viewing the degree of correlation between the anatomic infarct volume and the electrical infarct volume at each millisecond throughout ventricular activation In both the dogs exposed to nicotine and those who were not correlation between anatomic and electrical infarction size was maximal in mid ventricular activation For instance a correlation coefficient of 0 88 was established at 17 msec after the onset of activation in those dogs not exposed to nicotine and at 18 msec the best correlation coefficient of 0 86 was achieved in the nicotine exposed dogs Further the reproducibility of the electrical and morphologic techniques is supported by the similarity in the degree of correlation between the electrical infarct size and the anatomic infarct size when all dogs are considered as a group when those exposed to nicotine are considered alone and when those not exposed to nicotine were considered alone

Discussion

The increase in infarct size as the result of nicotine exposure is probably multifactorial and is certainly complex One consideration is the observation of the increased heart rate and ventricular arrhythmias confined to the first few minutes Recently a relationship between ven

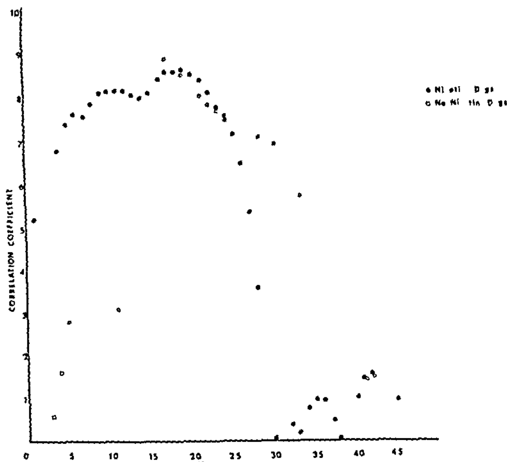


Fig 5 The degree of correlation between the anatomic infarct volume and the electrical infarct volume at each millisecond throughout ventricular activation is demonstrated. *The closed circles* represent the dogs exposed to nicotine and *the open squares* show the degree of correlation for the dogs not subjected to nicotine. Note the rising correlation in both groups from onset of activation. Best correlation occurred at msec 16, 17 and 18 in both groups with deterioration toward the end of activation.

tricular arrhythmias and infarct size has been emphasized. Certainly during the immediate early phase of nicotine administration the ventricular arrhythmias in the nicotine group were quite prominent, whereas ventricular ectopy occurring immediately after coronary occlusion had virtually disappeared in the group not exposed to nicotine. By 90 minutes post infarction, however, the groups were indistinguishable as far as ventricular ectopy was concerned. Therefore the period of difference in the incidence of ventricular arrhythmias was confined to the initial period of nicotine administration.

The effect of absolute size and the location of infarction as a predictor of arrhythmias is a consideration. It should be pointed out that these were relatively small infarctions. The occlusions were not of the proximal left coronary artery, which frequently produces ventricular fibrillation; rather they were more distally located and consistently at relatively the same site. We were not, then, confronted with either acute ventricular fibrillation and the subsequent need to defibrillate electrically, nor were we confronted with the early mortality often associated with acute infarction during the first four hours. Neither did our animals experience the sequels of extensive infarction resulting in a low cardiac output state with their consequent increase in endogenous catecholamines and the propensity for both ventricular arrhythmias and tachycardia related increase in infarct size.

We believe, therefore, that the extension of the infarct size with a single nicotine intervention probably is primarily the result of the dominant sympathomimetic pharmacologic response to the drug. Nicotine has a paradoxic effect in that depending on dose and route of administration it can result in slowing of the sinus node discharge as well. This was not observed in this series of

experiments The sinus tachycardia can be explained in part by discharge of epinephrine from the adrenal medulla resulting in an accelerated rate Additionally studies have demonstrated nicotine to result in the release of catecholamines from isolated organ preparations The sympathomimetic response to nicotine is contributed to further by the activation of chemoreceptors in the aortic and carotid bodies resulting in reflex vasoconstriction increased arterial blood pressure and tachycardia [9] Downey and colleagues [1] in a study of regional myocardial blood flow during nicotine infusion report that coronary vasodilation occurred in normal myocardium but in ischemic myocardium it increased only in proportion to aortic pressure This along with their observation in the presence of beta blockade of nicotine producing a further drop in cardiac output and rate and the abolition of previously present ventricular arrhythmias emphasizes the presence of nicotine s sympathetic effect [21]

Mean left atrial pressure rose much more markedly in animals rendered ischemic with left anterior descending artery ligation than in nonischemic controls Further aortic flow decreased by 12% This likely represents the increased impact of the peripheral sympathetic response on an already dysfunctional left ventricle

It is difficult to relate in either a supporting or a conflicting fashion the results of Downey and associates flow studies to our work Although nicotine increased flow in their ischemic model initially the transmural gradient across the myocardium was unchanged The flow increase seemed to be merely a function of an acute rise in aortic pressure While there was no evidence of shunting away from the ischemic zone certainly with aortic flow down and LV function compromised the increased flow state could be anticipated to be transitory

While the amount of nicotine administered 800 μg/minute is a large dose it is not an overwhelming dose considering the fact that some cigars today contain from 15 to more than 40 mg of nicotine and the acutely fatal adult dose is about 60 mg

It has been demonstrated that smokers who inhale may absorb up to 90% of the nicotine in the mainstream smoke drawn into their mouths [2] Further it has been demonstrated in cats and man that very comparable arterial levels of nicotine result from either inhaled or intravenously administered nicotine [3] The appropriateness of the model is further supported by work suggesting a predictable relationship between blood levels of nicotine and nicotine content in inhaled smoke

In addition to showing the increase in infarct size as a result of nicotine exposure this work offers further confirmation of the validity of using the difference map approach in estimating infarct size The consistency of finding in this series of 19 as in our earlier series of 10 that the best instant of correlation of electrical infarct volume with morphologic volume is between 16 and 18 msec is exciting We believe that this time during the course of ventricular activation is just prior to the time of the maximal wavefront reaching the epicardial surface When any technique of electrical subtraction is utilized one is actually attempting to specify the dimension of the zone of infarction Subtracting voltages occurring after infarction from control or baseline potentials results in the removal of all wavefronts outside the infarct zone Thus a subtrahend of infarction voltages is left The nearer this difference surface potential or infarction potential corresponds to the difference internal wavefront the better the correlation should be between the actual infarct extent and the difference potential By concentrating on mid activation and by restricting the method to instances without acquired major conduction defect one avoids the error introduced by loss of the basic endocardial to epicardial activation sequence Such loss would render comparisons invalid in left bundle branch block for instance and would render them valid only during early activation in right bundle branch block

In conclusion then this study had a twofold purpose First we wished to explore the effect of acute limited short term exposure to nicotine on the size of myocardial infarction We have demonstrated that nicotine acutely administered results in a significantly larger volume of infarcted muscle when all other variables are constrained as nearly as possible Secondly we set out to confirm whether the utility of infarct sizing employing body surface potential difference maps continued to demonstrate its good performance previously reported when a pharmacologic intervention had been imposed and a larger number of animals were considered We conclude that infarct size electrically determined

from the body surface difference map demonstrates a high correlation with the morphologically delineated infarct volume whether or not a pharmacologic intervention has been imposed The technique may prove useful in the assay of drug intervention as well as in surgical techniques employed in the modification of infarct size

The authors would like to acknowledge with appreciation the technical assistance of R Chris Hand

REFERENCES

1 Doll, R., and Hill A B Mortality in relation to smoking Ten years observations of British doctors Br Med J 1 1399 1460 1964
2 Shapiro S., Weinblatt E., Frank C W., and Sager R V Incidence of coronary heart disease in a population insured for medical care (HIP) Myocardial infarction angina pectoris and possible myocardial infarction Am J Publ Health 59(Suppl. 2) 1 1969
3 Spain D M and Bradess V A. Sudden death from coronary heart disease Survival time frequency of thrombi and cigarette smoking Chest 58 107 1970
4. Hill P., and Wynder E L. Smoking and cardiovascular disease Effect of nicotine on the serum epinephrine and corticoids AM HEART J 87 491 1974
5 Aronow W S Effect of cigarette smoking and of carbon monoxide on coronary heart disease Chest 70 514 1976
6. Flowers N C., Hand R C Sridharan M R., Horan L. G., and Sohi, G S Surface reflections of cardiac excitation and the assessment of infarct volume A comparison of methods Circ Res 43 406 1978
7 Snedecor G W., and Cochran W G Statistical Methods, 6th ed Ames Iowa 1976 Iowa State University Press pp 5 100
8 Cox J L. McLaughlin V W., Flowers N C and Horan L. G The ischemic zone surrounding acute myocardial infarction Its morphology as detected by dehydrogenase staining AM HEART J 76 650 1968
9 McLaughlin V W., Flowers N C Horan L. G., and Killam H A W The surface potential contribution from discrete elements of ventricular wall a closed chest d postmortem-documented prospective study Am J Cardi 1 34 302, 1974
10 Weast R C Selby S M., Hodgman C D eds Handbook of Mathematical Tables 2nd ed Cleveland Ohio 1964 Chemical Rubber Co p 5 9
11 Roberts R Husain A Ambos H D., Oliver G C Cox, J R., Jr and Sobel B F Relation between infarct size and ventricular arrhythmia Br Heart J 37 1169 1975
12. Allen J B and Laadt J R The effect of the level of ligature on mortality following ligation of the circumflex coronary artery in the dog AM HEART J 39 273 1950
13 Thomas M., Shulman G and Opie L. Arteriovenous potassium changes and ventricular arrhythmias after coronary artery occlusion Cardiovasc Res 4 327 1970
14. Bloor C M., Ehsani, A White F C., and Sobel B E Ventricular fibrillation threshold in acute myocardial infarction and its relation to myocardial infarct size Cardiovasc Res 9 468 1975
15 Page D L., Caulfield J B Kastor J A DeSanctis, R W., and Sanders C A Myocardial changes associated with cardiogenic shock N Engl J Med 285 133, 1971
16 Bolooki H., Lemberg L. Ghahramani, A., Economides, C Caldwell T., and Jude J R Clinical surgical, and pathologic correlations in patients with acute myocardial infarction and pump failure Circulation 44 1034 1971
17 Alonso D R Scheidt S Post M and Killip T Pathophysiology of cardiogenic shock Circulation 48 588 1973
18 Kent K M., Smith E R Redwood D R., and Epstein, S E Electrical stability of acutely ischemic myocardium Influences of heart rate and vagal stimulation, Circulation 47 291 1973
19 Han J., Garcia de Jalon P and Moe G K Adrenergic effects on ventricular vulnerability Circ Res 14 516 1964
20 Volley R L. and Koelle G B Ganglionic stimulating and blocking agents in Goodman and Gilman Eds Pharmacological Basis of Therapeutics 5th edition New York, 1975 Macmillan Publishing Co Inc pp 574
21 Downey H F., Bashour C A Boutros I S Bashour F A., and Parker P F Regional myocardial blood flow during nicotine infusion effects of beta adrenergic blockade and acute coronary occlusion J Pharmacol Exp Ther 202 55 1977
22. Armitage A K Dollery C T George C F Houseman, T H Lewis P J and Turner D M Absorption and metabolism of nicotine from cigarettes Br Med J 4 313 1975
23 Armitage A K The pharmacology of nicotine and tobacco smoking From Nicotine and Carbon Monoxide Symposium Symposium Proceedings 1 52, 197

Case reports

Atrial reentry in chronic repetitive supraventricular tachycardia

Jozsef Tenczer M D
Laszló Littmann M D
Ferenc Molnar M D
Ede Kékes M D
Budapest Hungary

Repetitive supraventricular tachycardia is a special arrhythmia characterized by shorter or longer runs of tachycardia separated by one or more sinus beats[1-4] It has generally been believed to reflect either reentrant mechanisms or rapid firing of ectopic foci In repetitive supraventricular tachycardia atrioventricular nodal reentry and reentry involving an accessory atrioventricular pathway have been demonstrated In this report a case of chronic repetitive supraventricular tachycardia is presented with reentry located within the atria

Case report

Electrophysiologic study of a ?8 year old woman was performed because of frequent episodes of tachycardia since 1967 After written consent of the patient was obtained His bundle electrocardiography and programmed atrial and ventricular stimulation procedures were carried out by approved techniques

Onset of the tachycardia ECGs during palpitation showed the pattern of repetitive supraventricular tachycardia Bouts of tachycardia were usually interrupted by four to ei ht sinus beats with P R intervals of 0 16 second and narrow QRS complexes (Fig 1) The tachycardia always started after gradual shortening of the sinus cycles at a critical P P interval of about 600 to 640 msec A H intervals of sinus beats provoking a run of tachycardia and of the preceding sinus beats were the same indicating that A H prolongation was no prerequisite to start a tachycardia (Fig 1) While spontaneous reappearance of the tachycardia was usually preceded by at least four sinus beats an atrial extrastimulus with an A A interval equal to or shorter than the critical P P interval could always induce the tachycardia even after the first sinus beat (Fig 2) Ventricular extrastimuli during sinus rhythm could neither provoke the tachycardia nor capture the atria The morphology of P waves during tachycardia differed from that during sinus rhythm but it was not of retrograde contour High right atrial electrograms preceded low atrial electrograms (Fig 3) excluding the possibility of retrograde atrial depolarization

Termination of the tachycardia The tachycardia was terminated by a spontaneous atrial extrasystole (Fig 4) Programmed atrial extrastimulation was performed to delineate the range of coupling intervals of atrial extrastimuli suppressing the tachycardia Atrial extrastimuli with A St intervals of 240 msec or longer could not and those with 220 msec or shorter coupling times could always terminate the tachycardia (Fig 5) In this figure it can also be noted that extrastimuli with longer coupling times are accompanied by wide QRS complexes while the extrastimulus with the shortest coupling time is not indicating a gap phenomenon in the left bundle branch conduction Progressive shortening of A A intervals of extrastimuli not suppressing the tachycardia resulted in progressive lengthening of the return atrial cycle A A as shown in Fig 6

Discussion

Mechanisms of repetitive supraventricular tachycardias can be delineated in clinical electrophysiology Tachycardias of ectopic origin show the following features (1) Early extrastimuli inserted during the tachycardia may enter the ectopic focus and reset its timing causing a pause less than compensatory (2) The tachycardia cannot be initiated and terminated by critically timed extrastimuli. In the described case these criteria for diagnosis of ectopic tachycardia were absent

The tachycardia in our patient was initiated and terminated by critically timed atrial extra

From the Third Dep rtm t f Medicine Semm lw is Uni rsity of Med ci nd Postgr duate Med cal School, Di isi n of Card logy

Rece ed f publication Oct 3 19 8
Accepted f r publ ation No 1 19 8

Reprint requests József Te cz M D Third Departm t of Medicin Semm lw is U rsity of Med in E t os u 1 H 1121 B d pest, Hu gary

Fig 1 Repetitive supraventricular tachycardia continuous tracings Paper speed 100 and 25 mm/second *HBE* His bundle electrogram *P* P wave of sinus beats *P'* P waves of tachycardia Note the differing P and P' contours and lack of A H prolongation at the onset of the tachycardia in the bottom strip

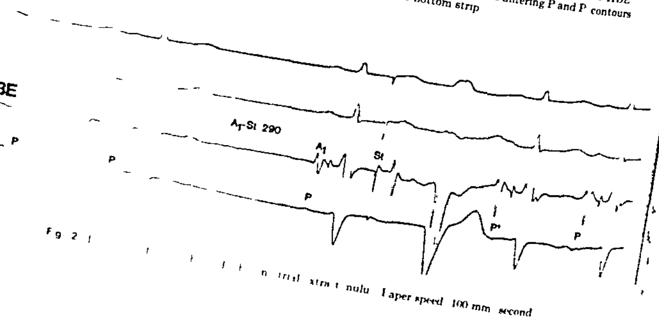


Fig 2 ... atrial extrastimulus Paper speed 100 mm second

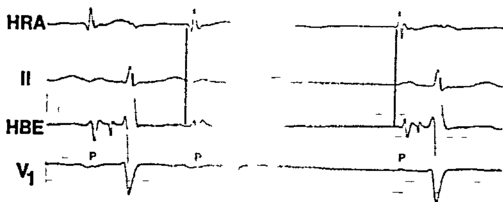


Fig. 3. Antegrade atrial activation sequence d[illegible] ir and tachycardia. *HRA* High right atrial electrogram. Paper speed 100 mm./second.

stimuli suggesting a reentrant mechanism. Lack of A-H prolongation preceding the tachycardia does not favor and the antegrade atrial activation sequence during tachycardia preclude an atrioventricular nodal reentry.[1] The relatively long R-P interval during tachycardia and inability of ventricular extrastimuli to capture the atria are against utilization of an accessory pathway for retrograde conduction to the atria.

Diagnostic criteria of atrial and sinus nodal reentry are identical apart from differences in P and A wave morphology and in atrial activation sequence.[1] In sinus node reentry the contours of P and A waves and the atrial activation sequence are identical with those during sinus rhythm. P and A waves in atrial reentrance should be different from sinus P and A waves and atrial activation depending on the site of the atrial reentry may be variable. In our case the changes in P and A wave morphology during supraventricular tachycardia favor atrial reentry.

Atrial reentry in repetitive supraventricular tachycardia—to our knowledge—has not been described so far.

Summary

Atrial reentrance as a mechanism of the tachycardia was demonstrated in a 28 year old patient suffering from chronic repetitive supraventricular tachycardia. Criteria for diagnosis included the following: (1) Repetitive supraventricular tachycardia was induced and terminated by properly timed atrial extrastimuli. (2) Return cycles of all atrial extrastimuli not abolishing the tachycardia were fully compensatory. (3) A-H prolongation was not a prerequisite to induce the tachycardia. (4) The contours of P and A waves during tachycardia differed from those in sinus rhythm, but atrial activation remained antegrade. (5) A concealed anomalous pathway could not be proved.

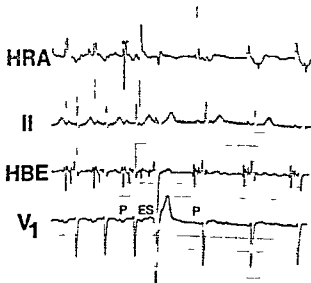
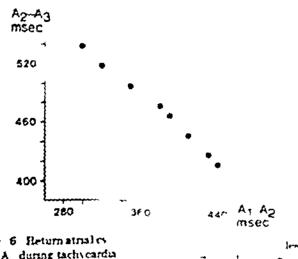


Fig. 4. Termination of the tachycardia by a spontaneous atrial extrasystole. *ES* Paper speed 25 mm./second.

Fig 5 Termination of the tachycardia by critically timed atrial extrastimuli. Paper speed 100 mm/second. An atrial extrastimulus with A St interval of 240 msec (A) did not and those with A St intervals of 220 msec or shorter (B and C) did terminate the tachycardia. Note that the A St interval of 160 msec was accompanied by an H H interval of 350 msec followed by a narrow QRS complex (C) in contrast to extrastimuli with longer coupling times (A and B) which resulted in a left bundle branch block QRS (gap in left bundle branch conduction).



6 Return atrial es… A during tachycardia

REFERENCES

1 Parkinson J and Papp C Repetitive paroxysmal tachycardia Br Heart J 9 241 134
2 Coumel Ph Junctional reciprocating tachycardias The permanent and paroxysmal forms of A V nodal reciprocating tachycardia J Electrocardiol 8 3 197
3 Krikler D Curry P Attuel P and Coumel Ph "Incessant" tachycardias in Wolff Parkinson White syndrome I Initiation without antecedent extrasystoles or PR lengthening with reference to reciprocation after shortening of cycle length Br Heart J 38 885 19
4 Arbel E R Cohen H C Langendorf R and Glick G Successful treatment of drug resistant atrial tachycardia and intractable congestive heart failure with permanent coupled atrial pacing Am J Cardiol 41 336 19
Scherlag B J Lau S H Helfant R H Berkowitz W D Stein E and Damato A N Catheter technique for recording His bundle activity in man Circulation 39 13 1969

6 Durrer D Schoo L Schuilenburg R M and Wellens H J J The role of premature beats in the initiation and the termination of supraventricular tachycardia in the Wolff Parkinson White syndrome Circulation 36 644 1967
7 Gillette P C and Garson A Jr Electrophysiologic and pharmacologic characteristics of automatic ectopic atrial tachycardia Circulation 56 571 1977
8 Goldreyer B N Gallagher J J, and Damato A N The electrophysiologic demonstration of atrial ectopic tachycardia in man Am Heart J 85 205 1973
9 Wu D and Denes, P Mechanisms of paroxysmal supraventricular tachycardia Arch Intern Med 135 437 1975
10 Coumel Ph and Barold S S Mechanisms of supraventricular tachycardia, in Narula O S., editor His Bundle Electrocardiography and Clinical Electrophysiology Philadelphia 1975 F A Davis Co., p 203
11 Goldreyer B N and Damato A N The essential role of atrioventricular conduction delay in the initiation of paroxysmal supraventricular tachycardia Circulation 43 679 1971
12 Wu D Amat y Leon F., Denes P., Dhingra R C., Pietras R J and Rosen K M Demonstration of sustained sinus and atrial re-entry as a mechanism of paroxysmal supraventricular tachycardia Circulation 51 234 1975

Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978 Therefore all manuscripts must be accompanied by the following written statement signed by one author The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C V Mosby Company in the event the work is published The undersigned author warrants that the article is original is not under consideration by another journal and has not been previously published I sign for and accept responsibility for releasing this material on behalf of any and all co authors Authors will be consulted when possible regarding republication of their material

Congenital atresia of the left coronary ostium and hypoplasia of the left main coronary artery

Craig J Byrum, M D
Marie S Blackman M D
Bernard Schneider M D
Henry M Sondheimer M D
Rae Ellen W Kavey M D
Syracuse N Y

Anomalies of the coronary arteries are not common comprising less than 46 per cent of congenital malformations of the heart[1] The case to be reported is a rare congenital malformation of the coronary arteries atresia of the left coronary ostium with hypoplasia of the left main coronary artery A single coronary system results which is not a true anatomical single coronary artery In addition the clinical and angiographic findings may be confused with anomalous origin of the left coronary artery from the pulmonary artery

Case report

A six month old female infant was admitted to the Pediat Unit of Crouse Irving Memorial Hospital with a two-day history of progressive respiratory distress Prior to this illness the patient had been completely asymptomatic with normal growth and development Birth and family history were unremarkable The infant appeared acutely ill and on physical examination was mottled gray with shallow respirations pulse 180 respiratory rate 80 blood pressure faintly audible at 100/60 Examination of the head and neck was unremarkable The lungs revealed rhonchi no râles were heard The heart was enlarged to percussion the heart tones were of poor quality with a gallop rhythm at the apex A faint ejection systolic murmur was heard at the left sternal border There was hepatomegaly 3 cm below the right costal margin All peripheral pulses were diminished

The pertinent laboratory findings revealed an elevated white blood count of 16 000 with a slight shift to the left The arterial blood gases were pH 7.35 PCO 38 PO 9 and arterial saturation of 79 per cent The cardiac enzymes 1? hours after admission revealed a CPK of 9 630 SGOT of 88 and an LDH of 996

The electrocardiogram taken on admission (Fig 1) demonstrated the pattern seen in anterior lateral wall myocardial infarction There was inversion and marked ST segment depression in Lead I and in the left precordial leads A deep Q was present in Lead aV_1

The x ray examination (Fig 2) revealed marked cardiomegaly and the vascular pattern was consistent with pulmonary venous congestion

The patient was digitalized placed in oxygen and cardiac catheterization was performed on the first hospital day (Table I) The data were consistent with poor myocardial performance There was no evidence of left to right shunting The right atrial and pulmonary artery pressures were moderately elevated There was a marked elevation of left atrial pressure and left ventricular end diastolic pressure

Angiograms were interpreted as consistent with the diagnosis of anomalous origin of the left coronary artery from the pulmonary artery The left atrial angiogram (Fig 3) revealed dilated left atrial and left ventricular chambers There was akinesis of the anterior and lateral walls as well as the apex of the left ventricle An aortic root angiogram (Fig 4) showed filling of a large right coronary artery arising from the anterior aortic cusp There was delayed opacification of a small, delicate left main coronary artery via collaterals from the right coronary artery The anterior descending and circumflex arteries both filled from the collaterals The high posterior position of the reconstituted main left coronary artery was consistent with the location encountered with anomalous origin of the left coronary from the posterior cusp of the pulmonary artery However the main pulmonary artery did not opacify on the aortic root injection and a pulmonary artery arteriogram did not demonstrate filling of a coronary vessel

Open heart surgery was performed The left coronary artery did not arise from the pulmonary artery as expected There was atresia of the left coronary ostium and marked hypoplasia of the left main coronary artery The left circumflex artery appeared normal The left anterior descending artery was extremely small and would not accept a graft An attempt was

From the Di n of Card l g Dep   Pediatri Upst t Medical C nt r Syracuse N w Y rk   d the D rtment f R d ol ogy Crouse-Irving Memorial H p al

Recei ved f r publi tion N

Accepted for public tion Dec

Reprint requests Dr M Bla kn   Irving Avenue Syracuse N Y 13210

00?? 8703/80/0303?4 + 0.?00 ?0/0 © 1980 The C V Mosby Co

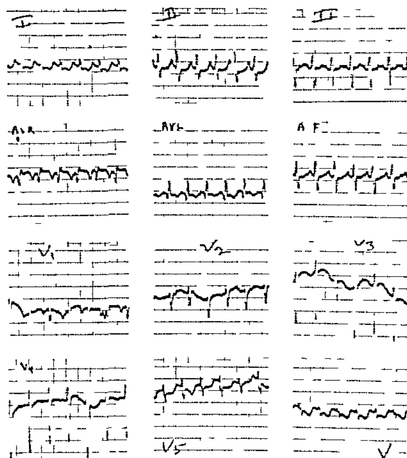


Fig 1 Electrocardiogram demonstrating an anterior lateral wall myocardial infarction



ı 2 X ray on admission demonstrating cardiomegaly and
lmonary venous congestion



Fig 3 Frontal film of left atrial angiogram with the left ventricle in end systole There is anterior apical and anterior septal akinesis



Fig 4 A and B The frontal (*A*) and lateral (*B*) aortic root angiogram demonstrates normal origin of a large right coronary artery There are septal collaterals from the right to left coronary artery Observe the reconstituted anterior descending circumflex and main left coronary artery Sequential films showed delayed filling via collaterals Note high posterior position of main left coronary artery

Table I Cardiac catheterization data

Site	*Pressure mm Hg systolic/ diastolic*	*m = mean*	*O saturation ( )*
Superior vena cava	—	—	56
Right atrium	1?/6	10	5?
Right ventricle	?0 ?0	—	48
Main pulmonary artery	4?/13	30	43
Left atrium	31/19	?1	8?
Left ventricle	84/?6	—	8?
Aorta	8?/41	??	?4 (on O)

made at dilatation of the left coronary ostium The patient did not survive the surgery

At autopsy the heart was markedly enlarged The right coronary artery appeared normal The left circumflex artery was normal arising from the atretic left main coronary The left anterior descending branch was small measuring 1 mm *The left coronary ostium* admitted a probe with difficulty There was a large left ventricular myocardial infarct of recent origin involving the apex lateral wall and a portion of the ventricular septum The microscopic examination of the left main coronary artery revealed a f [illegible] f [illegible] diminished elastica on the wall adjacent to the [illegible]

Discussion

Non patency of the left coronary ostium associated with atresia of the proximal left main coronary has been infrequently described in the literature as an isolated finding Only recently has it been included in a classification of primary congenital anomalies[1] of the coronary arteries It has been reported[1] in association with other congenital malformations of the heart and in some systemic diseases It is absent from most reviews of coronary artery occlusive disease and myocardial infarction in infancy and childhood including Stryker s frequently quoted review[1] which outlines eight categories of occlusive coronary disease No description of atresia of the left main coronary artery and ostium specifically appears in his discussion More recent discussions of occlusive congenital coronary artery disease and myocardial infarction in infants and children also contain no mention of the lesion A case very similar to the patient presented is reported in a textbook discussion by Lurie and represents the first inclusion of this lesion in a formal categorization of congenital anomalies of the coronary arteries producing occlusion and myocardial infarction Levin and associates in the most recent series of cases of congenital coronary artery disease also formally document and separately classifies this entity

In addition to the above two cases there have been five case reports in the literature which fi

the description of the case of Lurie[3] and our own case. Mullins and co-workers[1] describe a case in a ten-year-old male who underwent successful aortocoronary bypass grafting. The case of Fortuin and Roberts[11] in a 60-year-old male who was diagnosed at autopsy following sudden death attests to the fact that the lesion spans a wide age range and has unpredictable morbidity and mortality. MacMahon and Dickinson[1] describe the case of a six-week-old with myocardial infarction who at autopsy revealed non-patency of the right coronary ostium and stenosis of the proximal segments of both the right and left coronaries. The case of Goormaghtigh and colleagues[1] in a nine-year-old female was discussed in the context of an unproven infectious process and labeled as idiopathic. The autopsy findings demonstrated non-patency of the left coronary ostium associated with atresia of the first 1 cm of the left main coronary artery and stenosis of the right coronary ostium. This case is similar to ours and we believe represents a primary congenital anomaly of coronary arteries. There has been confusion in the literature in the distinction between the entities of congenital atresia of the coronary ostium and proximal coronary arteries and true single coronary artery. This is typified by the report of Murphy[1] entitled "Single Coronary Artery." He describes a 71-year-old male in whom the pathologic findings are actually identical to the cases of atresia of the left coronary ostium and hypoplasia of the proximal portion of the left coronary artery described above.

The paper by Fortuin and Roberts considers the possibility that atresia of the coronary ostium and hypoplasia of the proximal coronary artery segment may be one of the causes of true single coronary artery. However, reviews[1] of the subject of congenital single coronary artery in man contain no cases where an atretic proximal coronary artery was found. Some of the cases described did have dimples at the site of the absent coronary ostium. Embryologically it is suggested that single coronary arteries arise by failure of development or displacement of one coronary anlage. The developmental defect in congenital atresia of the coronary ostia and hypoplasia of the proximal main coronary artery segments may be similar to that producing true single coronary artery, but the resultant malformations are anatomically and clinically distinctly different.

Cardiac angiography should be a useful diagnostic tool to delineate the lesion in this report. However, both our case and the case described by Lurie[3] were diagnosed preoperatively as anomalous origin of the left coronary artery from the pulmonary artery. The criteria by cardiac catheterization for the diagnosis of anomalous origin of the left coronary artery from the pulmonary artery has been outlined and include retrograde filling of the left coronary artery through collaterals with opacification of the pulmonary artery on aortic root injection, the presence of a negative jet in systole or forward flow in diastole into the anomalous left coronary on pulmonary root injection, and left-to-right shunting by oximetry at the main pulmonary artery level. The absence of these findings in a suspected case of anomalous origin of the left coronary artery from the pulmonary artery should suggest the possibility of the lesion under discussion. But it should be recognized that anomalous origin of the left coronary artery from the pulmonary artery with poor collateral flow may not meet these criteria. Additionally, the presence of a short left main coronary artery filling retrograde and ending blindly should be diagnostic of congenital atresia of the ostium and hypoplasia of the left main coronary. Differentiating between the two conditions is of surgical importance but may not be possible clinically or angiographically.

In summary, the entity of congenital atresia of the coronary ostium and proximal left main coronary artery should be added to formal classification of primary congenital lesions of coronary arteries which cause occlusive coronary disease and/or myocardial infarction in infancy and childhood. As an isolated event, the lesion can be unilateral or bilateral and probably represents a failure of development of the coronary artery anlage. Pathologically it has been confused with congenital single coronary artery and clinically it can mimic anomalous origin of the coronary artery from the pulmonary artery. Absence of the usual catheterization and angiographic findings for anomalous origin of the left coronary from the pulmonary artery should raise the diagnostic possibility of congenital atresia of the coronary ostium and hypoplasia of the proximal main left coronary artery.

Summary

The clinical and pathological findings are described in a six-month-old female with unusual congenital malformation, atresia of

Fig 4 A and B The frontal (*A*) and lateral (*B*) aortic root angiogram demonstrates normal origin of a large right coronary artery There are septal collaterals from the right to left coronary artery Observe the reconstituted anterior descending circumflex and main left coronary artery Sequential films showed delayed filling via collaterals Note high posterior position of main left coronary artery

Table I Cardiac catheterization data

Site	Pressure mm Hg systolic/diastolic	m = mean	O saturation (%)
Superior vena cava	—	—	[illegible]6
Right atrium	1[illegible]/6	10	[illegible]
Right ventricle	[illegible]0/20	—	48
Main pulmonary artery	4[illegible]/13	30	43
Left atrium	31/19	21	8[illegible]
Left ventricle	84 [illegible]	—	87
Aorta	[illegible]/41	[illegible]2	94 (on O)

made at dilatation of the left coronary ostium The patient did not survive the surgery

At autopsy the heart was markedly enlarged The right coronary artery appeared normal The left circumflex artery was normal arising from the [illegible] left main coronary The left anterior descending branch was small measuring 1 mm The left coronary ostium [illegible] [illegible] with difficulty There was a large left ventricular [illegible] [illegible] origin [illegible] [illegible] [illegible] of the ventricular septum The microscopic examination of the left main coronary artery revealed [illegible] [illegible] elastica on the wall adjacent to the [illegible]

Discussion

Non patency of the left coronary ostium associated with atresia of the proximal left main coronary has been infrequently described in the literature as an isolated finding Only recently has it been included in a classification of primary congenital anomalies[1] of the coronary arteries It has been reported in association with other congenital malformations of the heart and in some systemic diseases It is absent from most reviews of coronary artery occlusive disease and myocardial infarction in infancy and childhood including Strykers frequently quoted review which outlines eight categories of occlusive coronary disease No description of atresia of the left main coronary artery and ostium specifically appears in his discussion More recent discussions of occlusive congenital coronary artery disease and myocardial infarction in infants and children also contain no mention of the lesion A case very similar to the patient presented is reported in a textbook discussion by Lurie and represents the first inclusion of this lesion in a formal categorization of congenital anomalies of the coronary arteries producing occlusion and myocardial infarction Levin and associates in the most recent series of cases of congenital coronary artery disease also formally documents and separately classifies this entity

In addition to the above two cases there have been five case reports in the literature which f

Heparin and atherosclerosis A review of old and recent findings

Hyman Engelberg M D
Beverly Hills Calif

Atherosclerotic disease and its complications are the leading cause of death in most advanced nations The medical profession therefore logically is interested in the prevention of atherosclerosis and the amelioration of this modern epidemic The current debate as to the relative merits of medical versus surgical therapy to retard the progress of established coronary disease attests to this interest There is considerable experimental and clinical evidence older and more recent which indicates that heparin would be useful in the prophylaxis and therapy of atherosclerosis Since this evidence is rarely discussed a valuable additional modality for clinical atherosclerotic disease may be overlooked

For several decades following discovery of the naturally occurring anticoagulant named heparin[1] investigators only concerned themselves with its chemical nature extraction from animal tissues and its use as an anticoagulant Interest in heparin in relation to atherosclerosis dates from the accidental observation in 1943 that heparin abolished post alimentary lipemia in dogs in vivo This did not occur when heparin was added to lipemic blood in vitro indicating the essential role of a tissue factor in the process These findings were soon confirmed in other animals and in man It was then shown that pre heparin lipemic plasma was cleared in vitro by the addition of plasma withdrawn after the injection of heparin in vivo establishing the presence of a lipemia clearing factor in the blood produced by heparin injection Ultracentrifugal methods revealed that an injection of heparin in rabbits and in man was followed by a rapid disappearance of the larger triglyceride rich lipoproteins from the plasma[5] a loss of neutral fat from the blood an absolute increase in alpha or high density lipoproteins and a shift in cholesterol from the beta to the alpha lipoproteins

The mechanism underlying these significant lipid changes became more clear when it was found that the post heparin lipemia clearing factor caused the lipolysis of triglycerides into free fatty acids and glycerol The role of serum albumin as the carrier molecule for the free fatty acids was recognized The active lipolytic substance was then extracted from rat heart and since it was active upon triglyceride rich lipoprotein substrates rather than upon simple triglycerides the enzyme was named lipoprotein lipase At the same time a lipemia clearing factor was found in some human plasmas without the prior injection of heparin This plasma factor was then shown to be lipolytic in nature and its identity with post heparin lipoprotein lipase and its distinction from pancreatic lipase was established The demonstration of the active lipolytic enzyme in tissues and blood without the prior injection of heparin proved that it was a normal physiologic substance a point previously in question

Subsequent work has shown that several other lipolytic enzymes appear in the blood after heparin injection However lipoprotein lipase is the major one and the results of many investigations have established that lipoprotein lipase enzymatic activity is the major physiologic pathway for the removal of triglycerides from the blood stream This applies to alimentary triglycerides transported in the blood as chylomicrons and to hepatically synthesized triglycerides transported as very low density lipoproteins It is ger

Received for publication Dec 19 8
Reprint requests Hyman Engelberg M D 465 North Roxbury Dr Suite 1003 Beverly Hills Calif 90210

0002-8703/80/030359 + 14$01.40/0 © 1980 The C V Mosby Co

accepted that the bulk of circulating triglycerides is hydrolyzed at the capillary endothelium However some circulating endogenous lipolytic activity has been found in the majority of normal individuals when platelet rich plasma was tested [1] In a few people this plasma lipolytic activity is substantial [1]

Although a highly purified lipoprotein lipase obtained from rat post heparin plasma and apparently essentially free of heparin, effects the hydrolysis of lipoprotein triglycerides much evidence indicates that endogenous heparin normally plays a role in the lipoprotein lipase mechanism Lipoprotein lipase is inhibited by heparin binding agents [1] Bacterial heparinase reduces the activity of chicken adipose tissue lipoprotein lipase The intravenous injection of a potent heparin antagonist in man resulted in a rise of fasting serum triglycerides [1] Circulating heparin binding immunoglobulins are associated with markedly increased serum triglyceride levels Lipoprotein lipase is released from its tissue sites by and is loosely bound to heparin The bond is probably ionic and reversible [1] Heparin also stabilizes the activity of the enzyme [1] and binds it to its substrate the triglyceride rich lipoprotein the negatively charged groups of heparin probably complexing with the ...vely charged amino groups of the lipopro... The role of heparin in facilitating the ...olysis of lipoprotein triglyceride via lipoprotein lipase bears much resemblance to its function in catalyzing the reaction between antithrombin III and plasma coagulant proteins

This brief summary of the probable role of endogenous heparin activity in the removal of triglyceride from the blood was necessary since defects in or interference with this physiologic pathway are important in the genesis of hypertriglyceridemia and those hypercholesterolemic states which are secondary to it There is evidence that such defects and interferences do exist

An earlier monograph presented the results of numerous investigations which using fat tolerance tests showed that there is a delay in the removal of ingested fat from the blood in atherosclerotic patients thus contributing to the increased serum lipids found in these individuals One of the factors that could play a role in such delay would be an inadequate amount of circulating endogenous heparin The normal presence of chemically defined heparin in the bloodstream in man has never been proven It has been shown in rat blood [1] However an extract has been obtained from normal human plasma which has the biologic activity of heparin In 1947 ...3 milligrams of such material was isolated from ... liters of human plasma using the standard method of extraction of heparin from animal tissues In 1954 an anticoagulant heparin like substance was isolated from small quantities of human plasma [1] and the next year increased yields were obtained [1] The material had the same biologic activity as commercial heparin It had anticoagulant activity in sheep plasma it enhanced antithrombic cofactor activity and its anticoagulant activity was neutralized by protamine Furthermore the plasma extract was strongly metachromatic with toluidine blue after prolonged dialysis and moved identically with commercial heparin on electrophoresis using toluidine blue paper It inhibited the generation of intrinsic plasma thromboplastin [1] It is possible that the extract contained other mucopolysaccharides besides heparin However the one closest to heparin is heparan sulfate and it has only about ten per cent of the anticoagulant potency of heparin Also recent x ray fiber diffraction studies have shown that approximately 20 per cent of the heparan sulfate molecule is identical to heparin It is probable that the heparin like activity of heparan resides in its heparin moiety Thus from the standpoint of physiologic function it matters little whether the extract obtained from normal human plasma is heparin or heparan or both Nor does it matter that heparin may not be a homogeneous substance What is important is that biologic heparin activity normally is present in human plasma

Quantitation of the anticoagulant activity in the plasma extract from clinically normal individuals showed that plasma heparin activity varied from 1 to 24 units per ml or from 1 to 2 4 mg heparin per liter of plasma a value very close to that obtained in 1947 This level of heparin activity though low is physiologically significant since only 01 unit of heparin in 0 8 ml of normal human plasma markedly accelerates the inhibition of activated factor X by antithrombin More relevant is the finding of an inverse relationship between endogenous plasma heparin activity and the triglyceride bearing very low density (Sf12 400) serum lipoproteins The results were statistically highly significant but

the relatively low correlation coefficient indicated that other factors in addition to the level of plasma heparin activity affected the lipoprotein levels It is unfortunate that these findings have not been investigated by others using reliable methods for the determination of circulating endogenous heparin activity since they are both physiologically and clinically significant They suggest that hypertriglyceridemia with its associated hypercholesterolemia and enhanced atherogenesis may result in part from a deficiency of circulating heparin activity analogous to the insulin deficiency present in some diabetic subjects Studies of mast cells in experimental animals have also led to the suggestion that a high susceptibility to atherosclerosis might be related to a deficiency of endogenous heparin[4]

Studies of circulating and tissue lipoprotein lipase activity have also given evidence of a relation of this normal enzymatic pathway to hypertriglyceridemia The triglyceride bearing very low density lipoproteins (Sf12 400) were statistically significantly lower in individuals who had demonstrable endogenous plasma lipemia clearing activity Lower lipoprotein lipase activity associated with the beta lipoproteins was found in patients with essential hyperlipidemia Adipose tissue lipoprotein lipase activity was inversely related to the level of serum triglycerides[1] Subjects with hypertriglyceridemia have lower values of heparin released lipoprotein lipase activity[5] Various types of abnormalities have been reported which interfere with efficient operation of the heparin lipoprotein lipase mechanism and result in increased serum triglycerides Chylomicra and larger lipoproteins resistant to the action of lipoprotein lipase have been described Absence of post heparin lipolytic activity was reported A qualitative defect in post heparin lipoprotein lipase was found in three siblings with hyperchylomicronemia

There have also been articles describing circulating inhibitors of heparin and lipoprotein lipase in atherosclerotic patients with increased lipids Some apoproteins interfere with the activation of lipoprotein lipase and a highly purified glycoprotein inhibitor of postheparin lipoprotein lipase and bovine milk lipoprotein lipase has been described Earlier studies had shown that thrombin extracts of white blood cells and platelets and human tissue extracts inhibited lipolysis to some extent Circulating clotting factors and lipoproteins compete for heparin The addition of lipoproteins to a mixture of heparin and serum prevented the activation of antithrombin[61] Thus an increased concentration of certain lipoproteins can cause hypercoagulability Conversely if coagulation factors are increased there might be inadequate heparin activity available to properly activate the lipoprotein lipase mechanism and hypertriglyceridemia would result The subject obviously requires much further investigation

Now we can discuss how injected heparin may act to retard the atherosclerotic process To begin with if a relative inadequacy of or interference with heparin activity are factors in many subjects with increased serum triglyceride levels supplying additional exogenous heparin is logical It is *analogous to the use of insulin in diabetes corti*costeroids in adrenal insufficiency or thyroid extract in hypothyroidism Apart from that many of the known actions of heparin would be beneficial in retarding the atherosclerotic process and its complications These actions of heparin can logically be divided into two categories

1 Effects at the vascular endothelial surface

2 General effects within the circulating blood

In some areas the two broad categories overlap Of course in relation to the atherosclerotic process ultimately all effects are on the arterial wall itself Let us therefore first consider actions of heparin at the vascular endothelium

Earlier work had suggested that injected heparin had an affinity for endothelium Uptake of heparin at the endothelial cell junctions was shown by various investigators[64,6] Tissue culture studies using human and animal endothelial cells showed that metachromatic heparin granules localized on the cell membrane surface Recently this important point has been confirmed Heparin was recovered from the endothelium in rats after its injection by the intravenous intraperitoneal or subcutaneous routes[6] There was a much greater concentration of heparin on the endothelium than in the blood When the aortic or venous endothelium of dogs rabbits or rats was exposed to dilute heparin solutions there was a very effective uptake of heparin by the endothelium This took place even when *the contact* with heparin was less than one minute and the endothelial heparin was much more concentrated than

the heparin in the surrounding medium Heparin was not removed after endothelial fixation by 10 to 20 washings with Locke s solution It is not known how long this fixation of heparin at the endothelium persists but it is apparently for much longer than anticoagulant activity can be demonstrated in the blood When exogenous heparin is taken up by mouse peritoneal macro phages the heparin containing granules are pres ent for about three weeks Recent studies using radioactively labelled heparin also showed that heparin has a high binding affinity for human endothelial cells even when excessive amounts of other glycosaminoglycans were present This binding affinity corresponded to about 10 hepa rin molecules per endothelial cell Other findings suggested that the heparin was bound to the surface of the endothelial cells and was not extensively degraded since it retained the ability to bind to antithrombin III The authors pointed out that endothelial heparin would anchor anti thrombin and so increase antithrombic activity at that site

Injected heparin localized and concentrated on the endothelial surface has many beneficial actions In the first place it may simply reenforce the physiologic functions of endogenous heparin activity at the normal vascular wall There are heparin containing mast cells immedi y beneath the endothelium of most blood vessels so that heparin is easily available at that site Metachromatic staining characteristic of heparin and heparin like substances is present on the vascular intimal surface of animals and man Antithrombic and antithrombo plas tin generating activity has been demonstrated in this metachromatic material of the vascular endothelium Heparin was identified electro phoretically in the glucose-aminoglycans isolated from the intima plus media of human aortic tissue Endothelial cells in tissue culture secrete mucopolysaccharides related to heparin the bulk of which is heparan Since heparan contains a heparin moiety heparin activity is normally present at the endothelial surface At this site there is evidence that it functions in the repair of injured vascular endothelium Normal intima has a negative electric potential which becomes positive after injury After heparin injection there is a marked increase in the electronegativity of the vascular intima apparently as a result of the absorption of heparin on the surface of the injured endothelium There is an inverse corre lation between the negative charge at the vascu lar interface and vascular injury in vivo

Exogenous heparin concentrated on the endo thelial surface would act to prevent endothelial injury It is accepted that the atherosclerotic process is enhanced and perhaps initiated at the sites of endothelial injury The intact endothe lium is a permeability barrier partially protecting the artery against atherogenic serum factors When it is damaged one of the earliest endothe lial reactions is contraction of the endothelial cells with consequent widening of the gaps between the cells and increased permeability to plasma atherogenic factors At the same time there is an increased sticking of platelets to the injured endothelial surface predisposing to thrombosis Heparin binds and inactivates many of the agents that injure endothelium Among these are histamine serotonin lysozyme angio tensin bradykinin some components of comple ment some viruses and many toxins Virus infections induce atherosclerosis in experimental animals and the disease resembles human athe rosclerosis Immunologic injury accelerates atherosclerosis especially when some degree of hyperlipidemia is present and heparin modifies a variety of allergic reactions Heparin minimizes platelet adhesion to damaged vascular endothelium and to artificial shunts Aggre gated platelets release various materials which may harm the vascular wall such as epinephrine serotonin lysosomal enzymes and cationic proteins Human platelets contain an enzyme capable of degrading a major part of the heparan normally associated with the endothelial cell surface This degradation was inhibited by heparin even though heparin itself was degraded by the enzyme A platelet factor also stimulates the proliferation of arterial smooth muscle cells which are key cells in atherogenesis Thus platelet adhesion to endothelium may enhance the athe rosclerotic process by injuring endothelium in various ways and by stimulating smooth muscle cell proliferation apart from the role of platelets in the initiation of arterial thrombi Injected heparin concentrated on the endothelial surface would minimize platelet adhesion and these harmful platelet effects

Apart from the protection against endothelial injury and platelet adhesion endothelial exoge nous heparin has a direct potent local anti

thrombic action. Injured endothelial cells and the exposed subendothelial tissue may initiate coagulation. The intima and media of human aorta have high thromboplastic activity, as does human atheroma material. Thus any intimal injury could release thromboplastic substances which could give rise to thrombin formation upon contact with the coagulation factors normally present on the vascular intima.

It is also probable that irreversible platelet aggregation and the platelet release reaction, which probably initiate arterial thrombi, are dependent on the generation of thrombin from the coagulation factors in the plasma surrounding the platelet surface. Thrombin itself produces endothelial injury, is a potent mitogenic agent, and increases platelet adhesion to the vessel wall. An anti-thrombin agent (hirudin) markedly decreased the adherence of thrombin-aggregated platelets to endothelial and smooth muscle cells. Platelets adhere to endothelial cells in culture after they have been treated with thrombin or activated factor X. Minute quantities of heparin prevent the activation of factor X. Endothelial heparin therefore would minimize thrombin formation and its effects at sites of endothelial injury. Heparin also markedly inhibited the intimal smooth muscle cell proliferation that resulted from vascular injury. Heparin was more effective than platelet-inhibiting drugs in preventing thrombus formation in experimentally injured carotid arteries. Another action of exogenous heparin at the endothelial surface should be mentioned. Minute amounts of heparin in the medium inhibited the uptake of serum lipids by human and animal arterial endothelial cells in tissue culture. Unfortunately, this has not been investigated by other workers. This effect, which would act to decrease the entrance of atherogenic serum lipoproteins into the vascular intima cells, probably results from the negative charge of heparin localized on the cell surface.

Let us now discuss the general effects of injected heparin in the circulation which might be important in relation to atherogenesis. We will first start with the effects upon blood lipids. As mentioned earlier in this article, the clearing of lipemia after heparin injection reflects a rapid disappearance of chylomicrons and very low density lipoproteins from the plasma resulting from the lipolysis of their triglyceride content, a decrease in circulating triglycerides, and an absolute increase in alpha or high density lipoproteins. In general, after a 20 000 unit injection of heparin subcutaneously, it takes about 48 hours for the lipid values to revert to their initial levels if a normal diet is ingested. These changes in the circulating lipids have several important effects.

To begin with, the reduction in the average level of circulating atherogenic lipoproteins results in a decreased insudation of these lipoproteins into the arterial wall, although the magnitude of this response is hard to quantitate. Decreased infiltration of atherogenic lipoproteins not only would slow the atherosclerotic process but might allow mechanisms of repair or regression to operate more efficiently. Increased lipidemia adversely affects the regeneration of injured arterial endothelial cells and can also produce primary endothelial injury.

Lipemia also has harmful effects within the blood itself which would be decreased when lipid levels are lower. Increased agglutination of erythrocytes with resultant capillary stasis has been observed after high fat meals. The infusion of fat emulsions accelerated coagulation as shown by thrombin generation tests, an action completely prevented by small doses of heparin. Fats increased the resistance of blood clots to lysis. This increased thrombotic tendency with increased lipemia may result from the effect on platelets. The latter are then more sensitive to thrombin-induced and to ADP-induced aggregation. Both saturated and unsaturated fats increase platelet adhesiveness in man, with saturated fats doing so to a greater extent. The action of fats on platelet adhesiveness is greater in patients with coronary disease than in healthy individuals. The correction of hyperlipidemia in patients with coronary heart disease increased their previously decreased platelet survival times.

Another harmful effect of increased serum lipids is that upon tissue oxygen supply. This important subject, which has relevance both to atherogenesis and to tissue and myocardial function, has been largely ignored. Before discussing it further, it is necessary briefly to consider how the oxygen demand of the arterial wall is met.

Oxygen is supplied to the arterial wall from the arterial lumen and from the vasa vasorum which nourish the outer two thirds of the vessel wall. The intima and inner media are entirely depen

dent on the diffusion of oxygen from the lumen In larger mammals and man the avascular wall thickness of large arteries is approximately 1 mm close to the limiting distance over which oxygen diffusion will adequately supply tissue needs Oxygen tension is lowest in the media with a sharp rise in the tissue just below normal endothelium Thus the media and its smooth muscle cells are constantly on the brink of hypoxia and are sensitive to alterations in oxygen tension In man due to intimal thickening the distance over which oxygen must diffuse to reach the media increases with age In addition early fatty lesions of atherosclerosis markedly interfere with oxygen diffusion through the intima These anatomic and physiologic considerations implicate the oxygen economy of the arterial wall in the pathogenesis of atherosclerosis Beyond this there is much evidence that hypoxia accelerates the atherosclerotic process

Does lipemia affect tissue oxygenation? The uptake of oxygen by the red blood cells of hypercholesterolemic rabbits was decreased Studies of forearm arteriovenous oxygen differences and then of total oxygen consumption in atherosclerotic patients showed an increase of tissue oxygen consumption after heparin from initial subnormal values almost up to normal The [illegible]crease in oxygen consumption did not occur at [illegible] time when clotting was most prolonged by [illegible]parin but coincided with maximal lipid clearing Oxygen inhalation oral anticoagulants and saline placebos had no such effect on oxygen consumption More recent studies using an ear oximeter showed an increase in the rate of oxygen transfer from blood to tissue after heparin in subjects with coronary atherosclerotic disease On the other hand intravenous fat emulsions slightly decrease arterial oxygen saturation in man and in experimental animals There is a decrease in skin oxygen tension in man coincident with postprandial lipemia with a rapid rise to normal levels after heparin In the non lipemic state heparin had no such effect Post alimentary lipemia prevented the usual enhancement of myocardial oxygen extraction after exercise These various studies indicate that lipemia impedes oxygen diffusion

There is evidence that suggests how this occurs Layers of fat particles at cell [illegible] may react with other substances and these [illegible] are altered by the degree [illegible] the molecules Due to their property of combining with oxygen fats affect estimates of the solubility or diffusion constants of oxygen The diffusion of oxygen through the blood plasma is also decreased by an increased concentration of plasma proteins and lipoproteins even over normal physiologic ranges Other possible mechanisms whereby abnormal concentrations of lipoproteins may affect oxygen utilization have been discussed elsewhere Whatever the mechanism the decrease in lipemia after heparin injection increases tissue oxygen supply

A relative and absolute reduction in the alpha or high density lipoproteins in patients with known coronary atherosclerotic disease was found long ago but its significance was overlooked until the past few years Several epidemiologic studies recently summarized provide good evidence that higher levels of high density lipoproteins are an independent protective factor against the development of atherosclerosis and contribute to increased longevity As mentioned earlier when heparin is injected one of the lipid changes is an absolute increase in the alpha or high density lipoprotein fraction Chemical analysis confirmed that a higher percentage of the total cholesterol was in the alpha lipoprotein fraction after heparin It was noted that the redistribution of lipids elicited by heparin injection was toward the pattern present in normal subjects without known atherosclerotic disease A current investigation is substantiating these results (unpublished data) In the majority of patients with coronary atherosclerosis high density lipoprotein levels or the percentage of the total cholesterol in the high density fraction are temporarily increased following a single injection of heparin This may well be another significant pathway whereby exogenous heparin is beneficial Unfortunately there are no studies of the effect of long term administration of heparin on HDL levels

Another channel via which exogenous heparin may act in relation to atherogenesis is by displacement of the major site of lipoprotein lipase action Normally the bulk of chylomicron and very low density lipoprotein triglyceride lipolysis probably occurs at the capillary surface The removal of triglyceride from the large lipid laden particles leaves cholesterol rich remnants and beta lipoprotein in high concentration at [illegible] within the endothelium Rat aortic medial

smooth muscle cells showed an enhanced uptake of these remnant particles. Thus it has been proposed that atherogenesis is linked to the normal interaction of endothelial lipoprotein lipase with triglyceride rich lipoproteins. Injected heparin displaces much of the enzyme into the plasma. A greater portion of triglyceride lipolysis then takes place within the circulating blood leaving a lower concentration of the cholesterol rich remnant particles at the endothelial surface available for endothelial cell uptake.

For many years there have been reports suggestive of an enhanced tendency to coagulation in atherosclerotic individuals. Clinicians have long been aware that some patients required much more heparin than usual to achieve therapeutic anticoagulation. Documentation of a hypercoagulable state has been difficult but has received support from more recent studies. Heparin resistance has been reported resulting from abnormal plasma globulins. Decreased antithrombin III and increased serum heparin neutralizing activity were found in survivors of myocardial infarcts. Increased platelet factor 4 levels in the blood were present in patients with thromboembolic states and in patients with severe coronary heart disease. Increased heparin neutralizing activity (platelet factor 4) is present in and released from aggregated platelets of men with established coronary heart disease. There is much slower disaggregation of such platelets probably resulting from the facilitation of thrombin generation when more heparin neutralizing factor is released. Low rates of platelet disaggregation also occur with greater frequency in patients with peripheral arterial disease. Patients whose platelets disaggregate slowly may be more likely to develop a thrombus when platelets contact exposed subendothelial connective tissue. As noted earlier lipoproteins interfere with the activation of antithrombin III by heparin. Small doses of heparin injected twice a week corrected the increased coagulability and platelet adhesiveness found in some patients with atherosclerotic disease. Estrogens decrease the activated factor X inhibitory activity of plasma without changing the level of antithrombin III and so produce a hypercoagulable state which is completely reversed by trace amounts of heparin. Heparin neutralizes may of the cationic proteins released by platelets, leukocytes, and other sources. These proteins influence blood coagulation and fibrin precipitation and so have potential significance in intravascular coagulation. The neutralization of a hypercoagulable tendency in the blood if present is another way in which injected heparin would benefit atherosclerosis particularly if microthrombi are involved in atherogenesis.

As stated earlier in this article endothelial injury probably is the initial prerequisite to the sequence of events leading to atherosclerotic lesion. The mechanisms leading to endothelial injury are not clear. It has been proposed that activated serum complement is a key factor involved in endothelial injury. The complement system is an effector pathway of the inflammatory response which normally is present in an inactive form in the bloodstream. It is activated specifically by infections and immune complexes or non specifically as by aggregation of macromolecules. Circulating immune complexes have been found in a substantial fraction of patients with vascular disease and their effect in activating complement may be a major pathway whereby immunologic injury accelerates atherosclerosis. The consequences of complement activation include increased vascular permeability, attraction to leukocytes, adherence of complement coated complexes to formed elements of the blood, and alterations in cell membranes that can lead to lysis and cell death. Recently it was shown that inhibition of the third component of complement by cobra venom decreased the extent of myocardial necrosis after coronary occlusion in experimental animals, illustrating the important role that complement can play in the inflammatory response even when activated non specifically.

Activation of the complement system results in the sequential interaction of the serum proteins or components of which it is composed. Since the complement system is potentially capable of producing drastic effects it has safeguards to control its activation. These include various inhibitors. It has long been known that heparin interfered with the action of complement. Early studies identified several possible sites of this inhibitory action by heparin ranging from classical early to late component functions. Recent studies confirm this. Normal serum has a protein called C1 esterase inhibitor which inhibits the activated first component of complement. Heparin at very low concentrations greatly poten

tiates the activity of this inhibitor and the authors noted that the kinetics of the effect were strikingly similar to those of the action of heparin plus antithrombin in the coagulation sequence. Complement activation involves amplification of the third component of complement via the formation of an amplification convertase. Both commercial and native rat mast cell heparin inhibit the generation of this amplification convertase, which may well determine whether the initial activation of the complement sequence by the classical or by the alternative pathway eventuates in the effective utilization of the terminal components. The classic pathway of complement activation is progressively inhibited by increasing concentrations of heparin whereas its effect in the alternative pathway is apparently more complex. Since complement activation involves a cascade of protein interactions similar to the coagulation cascade, since heparin in minute amounts immediately markedly potentiates the activity of a serum inhibitor of complement activation, it may not be too far afield to suggest that injected heparin perhaps reinforces a physiologic activity of endogenous plasma heparin. In any event, if the activation of complement is an important pathway of endothelial injury, injected heparin would at least partially inhibit it and so limit tissue damage.

These various effects of heparin at the endothe ... and in the bloodstream indicate that it would be valuable in the prophylaxis of atherosclerosis. What results have been obtained? In cholesterol fed animals the majority of investigators reported a substantial reduction in the extent of experimental atherosclerosis as compared to controls. Heparin also arrested the further development of pre established aortic atheroma despite continued cholesterol fat feeding. It retarded experimental atherosclerosis in endarterectomized iliac arteries. Heparitin sulfate (heparan), which has heparin like activity, also decreased the degree of experimental atherosclerosis. Negative results with heparin in retarding atherosclerosis in experimental animals also have been reported. It is possible that the extreme hypercholesterolemia attained in experimental animals and species and strain differences contributed to some of the negative findings.

Prophylactically in human ... with established coronary atherosclerotic disease, heparin has been given subcutaneously. From this site heparin is slowly released into the blood, thus providing low but persistent levels of circulating heparin which also give continued higher heparin concentrations at the endothelial surface. Most investigations of the use of long term heparin therapy in human subjects with prior acute myocardial infarction(s) have shown good results. Four of these were controlled studies. In the first, in which 20 000 units of concentrated aqueous heparin were injected subcutaneously twice a week over a two year period, there were four cardiovascular deaths in 105 patients on heparin as compared to 21 deaths in 117 patients who received placebo injections. The two groups of patients were comparable, and the difference in the annual mortality rate (2 4 per cent vs 11 5 per cent) was statistically definitely significant, $p = .01$. The next study compared full anticoagulant doses of heparin given twice daily with oral anticoagulant therapy over a two year period. The mortality rate in the heparin group (53 patients) was 5 6 per cent as compared to 15 7 per cent in the 51 patients on prothrombin depressing drugs. In the third study, 46 male patients received heparin 20 000 units twice a week and 43 men were given placebo injections for a six year period. Over that time there were seven acute myocardial infarcts and one death in the heparin group and 10 infarcts and six deaths in the placebo group. The difference in deaths was statistically significant. In the fourth controlled but smaller investigation, heparin was given in daily doses of 5 000 to 6 000 units subcutaneously and compared to oral anticoagulants. Over a 3 3 year period there was one cardiac death in the 30 patients in the heparin group (1 per cent annual mortality rate) as compared to 10 cardiac deaths over a 5 7 year period in the 18 patients on oral anticoagulants (9 to 10 per cent annual mortality rate). The difference in mortality was statistically significant. However, in this last study the patients were not fully randomly allocated as they were in the first three investigations. All four of the above were prospective studies.

Several uncontrolled studies have reported good results. Over an eight year period an annual mortality rate of 2 9 per cent was observed in 5... patients with advanced coronary heart disease who received 20 000 units of heparin twice weekly. Over a five year period in 116 patients on 10 000 units of heparin daily a 1 per cent annual mortality rate was noted. In a group of 61

patients who received 10 000 units of heparin every other day after an initial larger dose the first four weeks plus a low fat low cholesterol diet only one death was reported over a 3 to 9 year treatment period However, in this last study although all patients had angina only 19 of the 64 had a prior myocardial infarct

In two controlled investigations negative results were obtained In the first heparin 25 000 units twice a week was compared to oral anticoagulants Therapy was started upon discharge from the hospital after acute myocardial infarction After the first year heparin was discontinued as the mortality rate was no different on heparin than that of the control group The authors noted that the exclusion of the deaths in the first six months after infarction would have given results suggesting a favorable effect of heparin In the second negative trial therapy was also started upon discharge from the hospital after acute myocardial infarction Patients received 20 000 units of heparin (5 000 unit per ml) twice a week intramuscularly and results were compared to placebo injections This was a cooperative study involving nine medical clinics but it was unclear as to the details of randomization Over a 1 to 3 year average period of therapy there was no difference in mortality rate between the two groups

Careful analysis of all the controlled and randomly allocated studies reveals a logical explanation for the difference in results In the three that showed a long term protective effect of heparin therapy was started no sooner than six months and usually 1 to 2 years after myocardial infarction In the two negative reports treatment was begun upon discharge from the hospital after an acute myocardial infarction It is now appreciated that the majority of deaths in the first year after infarction result from disturbed electrical mechanisms or severe pump failure rather than from progress of the basic atherosclerotic coronary disease Heparin has no known effect upon myocardial electrical instability Therefore retardation of the atherosclerotic process would be less apparent in the first 1 to 2 years after an acute myocardial infarct

Heparin is a very safe medication and few serious reactions have been reported on long term intermittent therapy With subcutaneous smaller doses given more frequently as 5 000 units daily or 10 000 to 15 000 units every other day the risk of major hemorrhage or of rebound hypercoagulability is very low Repeated clottings tests are unnecessary Many physicians are of the opinion that the prolonged use of heparin causes osteoporosis A review of all reported cases showed that osteoporotic fractures have only occurred in adults who were given no less than 15 000 units of heparin daily for at least six months An increased incidence of fractures or of bone pain has not been noted in patients receiving intermittent heparin therapy nor have platelet counts been lowered (unpublished observations) The decrease in circulating antithrombin III recently reported in patients on continuous heparinization was not found when heparin was given intermittently although these subjects did not receive heparin subcutaneously

In view of the preceding discussion and the facts presented it is hard to understand why this subject has been ignored For years heparin has not even been mentioned as a possible additional modality in the prophylaxis of atherosclerosis in any leading article nor in statements by official medical advisory committees Perhaps the answer lies in an earlier excessive claim that a few injections of heparin relieved angina in the majority of patients a claim that was not verified Perhaps it lies in the widespread unjustified concern about osteoporotic fractures or hemorrhage Nevertheless although there are many unanswered questions the available evidence deserves attention Additional controlled clinical studies are needed The indications for treatment with heparin in relation to atherogenesis are not well established although they have been more fully discussed elsewhere However it would be unfortunate in view of the unsettled question of the relative merits of medical versus surgical therapy in prolonging the life of patients with coronary disease if an important medical modality were being overlooked

Summary

This article reviews the experimental and clinical evidence regarding heparin therapy in the prophylaxis of coronary heart disease The actions of heparin take place at the vascular endothelium where injected heparin concentrates and within the bloodstream At the endothelium heparin acts to prevent endothelial injury prevent thrombin generation prevent platelet

adhe ion to endothelium and to decrease uptake of serum lipoproteins Within the bloodstream heparin increases lipoprotein lipase activity and reduces the concentration of atherogenic very low density lipoproteins The reduction in lipemia enhances oxygen transfer from blood to the tissues and decreases thrombin or ADP induced platelet aggregation Heparin increases the concentration of high density lipoproteins It decreases hypercoagulability and inhibits overactivation of serum complement Heparin reduced atherosclerosis in most studies in cholesterol fed animals In human subjects who had a myocardial infarct at least one year before the onset of treatment long term intermittent heparin therapy significantly decreased cardiovascular deaths as compared to control groups

REFERENCES

1 McLean J The thromboplastic action of cephalin Am J Phys iol 41 250 1916
2 Hahn P F Abolishment of alimentary lipemia following injection of heparin. Science 98 19 1943
3 Weld C B Alimentary lipemia and heparin Can. Med Assoc J 51 578 1944
4 Anderson N G and Fawcett, B An antichylomicronemic substance produced by h parin injection Proc Soc Exp Biol Med 74 768 1950
5 Graham D M Lyon T P Gofman J W., Jones H B., Yankley A Simonton J and White S Blood lipids and atherosclero is II The influence of heparin upon lipoprotein metabolism Circulation 4 666 1951
6 Grossman M I The effect of heparin on the fate of intravenou ly admini tered fat emulsion J Lab Clin Med 40 805 195_
7 Brown W D Reversible effects of anticoagulants and protamine on alimentary l pemia Q J Exp Physiol 37 7 195_
8 Van E k W F Peters, J F and Man E B Signifi ance of la tescence in blood serum Metaboli m 1 383 19 _
9 Boyl F Bragdon J H and Brown R K Role of heparin in itro production of alpha 1 lipoproteins in human pla ma Proc Soc Exp Biol Med 81 475 19
10 Nikkila E Studies n the lipid-protein relation hips in n rmal and pathol gical sera and the effect of heparin n serum lipopr tein Scand J Clin Lab Invest 5 Suppl 8 19 3
11 Nich A V Freeman N K Sh re B and Rubin L Th int ra ti n f heparin acti fa tor and lipoproteins Circulati n 6 4 19
12 Gordon R S Jr B yl E Brown R K Cherkes, A., and Anf nser J B R le f serum lbumin in lipemia clearing rea ti Pr S E p Bi l Med 84 168 19 3
13 Robinson D S nd Fre h I F Th of serum albumin in the r ra i l r ma in the rat Q J Exp Ph i 38
14 Korn E D Properties f an r ed from rat heart acetone powd r Scie 120 1954
15 Engelberg H Studies n m lipemia clearing factor Circulati n 10 1954
16 Engelberg H Human endogenous lipemia clearing factor Am J Physiol 181 309 1955
17 Engelberg H Human endogenous lipemia clearing activity Studies of lipolysis and effect of inhibitors J Biol. Chem 222 601 1956
18 Engelberg H Incidence of endogenous lipoprotein lipase activity in human plasma Proc Soc Exp B l Med 116 422 1964
19 Engelberg H Studies of optimal condition f r the measurement of circulating endogenous lipoprotein lipase activity J Atheroscler Res. 10 353, 1969
20 Engelberg H In vitro studies of the lipolysis post alimentary lipemia in man Metaboli m 7 1 1958
21 Muir J R The regional production of lipoprote lipase in man Clin Sci 34 261 1968
22 Fielding P E Shore V C and Fielding C J Lipoprotein lipase Properties of the enzyme isolat from post heparin plasma Biochemi try 13 431 1974
23 Korn E D Inactivation of lipoprotein lipase t heparinase J Biol Chem 226 8? 19
24 Engelberg H The effect of a heparin antagonist c fasting serum triglycerides in man J Atheroscler Re 6 240 1966
25 Glueck C J Kaplan A P Levy R I Greten H Gralnick H and Fredrickson D S A new mechanism of exogenous hyperglyceridemia ANN Intern Med 71 1051 1969
26 Glueck, H I MacKenzie M R., and Glueck C J Crystalline IGG protein in multiple myeloma ident cation of effects on coagulation and lipoprotein m tab olism J Lab Clin Med 79 731 19
27 Beaumont J L and Beaumont V Autoimmun hyperlipidemia Atheroscleros 26 105 197
28 Engelberg H Human endogenous pla ma lipemi clearing and lipolytic activity after tricalcium phos phate absorption Proc Soc Exp Biol Med 95 39 1957
29 Engelberg H Studies indicating inactivation of p t heparin and endogenous human pla ma lipoprotein lipase during tri lyceride lipolysi Proc Soc Exp Bio Med 99 489 1958
30 Egelrud T Reversible binding of lipoprotein lipase from hen adipose ti ue to heparin Biochim Bioph Acta 296 124 1973
31 Fielding C J Purification of lipoprotein lipase f o rat post heparin pla ma Biochim Bi phys Act 178 499 1969
32 Korn E D., and Quigley T W Jr Lipoprotein lipa of chicken adipose ti ue J Biol Chem 226 195
33 Patten R L., and Hollenberg C H The mecha ism of heparin stimulation of rat adipocyte lipoprot in lip J Lipid Res 10 3 4 1969
34 Iverius I H The interaction between hum n pl m lipoproteins and connective tis ue glycosaminoglycans J Biol Chem 247 60 1972
35 Rosenberg R D Chemi try of the hemostati mecha ni m and its relati n hip to th actic n of heparin Fed Proc 36 10 1977
36 Engelberg H Heparin Metaboli m Phy i l g a d Clinical application Springfield 19 3 Cha les C Thoma Publi her
37 Horn r A A Demon trati n of end gen us heparin rat blood Adv Exp Med Bi l 52 5 1975
38 A trup T On th determination f h parin in H l pla ma and urine Acta Pharma ol Toxi l 3 1947

39 Freeman L, Engelberg H, and Dudley A: Plasma heparin levels. A method for the determination of plasma heparin based upon anticoagulant activity. Am J Clin Pathol 24:599, 1954

40 Nilsson I M, and Wenckert A: Demonstration of a heparin like anticoagulant in normal human blood. Acta Med Scand 150 Supp 279, 1954

41 Engelberg H, Dudley A, and Freeman L: An improved method for the determination of plasma heparin. J Lab Clin Med 46:653, 1955

42 Engelberg H: Effects of sulfated mucopolysaccharides and of endogenous plasma heparin in thromboplastin generation. Proc Soc Exp Biol Med 109:814, 1962

43 Atkins E D T, and Neiduszynski I A: Effect of alpha 1 iduronate conformation on the molecular shape of heparin. Fed Proc 16:78, 1977

44 Engelberg H: Plasma heparin levels in normal man. Circulation 23:578, 1961

45 Yin E T, and Wessler S: Heparin accelerated inhibition of activated factor X by its natural plasma inhibitor. Biochim Biophys Acta 201:387, 1970

46 Engelberg H: Plasma heparin levels. Correlation with serum cholesterol and low-density lipoproteins. Circulation 23:573, 1961

47 *Constantinides P: Mast cells and susceptibility to* experimental atherosclerosis. Science 117:505, 1953

48 Sue T K, and Jacques L B: Susceptibility to experimental atherosclerosis. Relation to mast cells and heparin. Atherosclerosis 25:137, 1976

49 Engelberg H: Human endogenous lipemia clearing activity. Observations in 482 individuals. J Appl Physiol 13:375, 1958

50 Hood B, Bedding P, and Carlender B: B lipoproteins, lipoprotein lipase and atromid. J Atheroscler Res 3:509, 1963

51 Persson B: *Lipoprotein lipase activity of human* adipose tissue in different types of hyperlipidemia. Acta Med Scand 193:447, 1973

52 Boberg J: Heparin released blood plasma lipoprotein lipase activity in patients with hyperlipoproteinemia. Acta Med Scand. 191:97, 1972.

53 Carlson L A, and Olhagen B: Studies on a case of essential hyperlipemia. J Clin Invest 38:854, 1959

54 Havel R J, and Gordon R Jr: Idiopathic hyperlipemia: metabolic studies in an affected family. J Clin Invest 39:1777, 1960

55 Bradford *R H and Furman R H: Plasma post* heparin lipolytic activity in hyperchylomicronemia (fat induced lipemia). Biochim Biophys Acta 164:172, 1968

56 Brown V W, and Baginsky M L: Inhibition of lipoprotein lipase by a apoprotein of human very low-density lipoproteins. Biochim Biophys. Res Comm 46:375, 1972

57 Wagh P V: Lipolipin. A glycoprotein inhibitor of post heparin lipoprotein lipase. Adv Exp Med Biol 52:281, 1975

58 Wagh P V, and Olivecrona T: The in vitro inhibition of bovine milk LL by a glycoprotein preparation from human atherosclerotic intima. Atherosclerosis 29:195, 1978

59 Pilgeram L O, and Tu A T: Thrombin inhibition of the lipoprotein lipase system. J Appl Physiol. 11:450, 1957

60 Fekete L L, Lever W F, and Klein E: Inhibition of lipemia clearing activity by human white blood cells and platelet components. J Lab Clin Med 52:680, 1958

61 Klein E, Lever W F, and *Fekete L L: Inhibitors of* lipemia clearing in tissues. J Invest. Dermatol 30:41, 1958

62 Hirsch R L, Kellner A, and Ireland R: Changes in blood coagulation during the clearing of lipid emulsions by lipoprotein lipase. J Exp Med 112:699, 1960

63 Bleyl, H, Addo O, and Roka L: Heparin neutralizing effects of lipoproteins. Thromb Diath Haemorrhag 34:549, 1975

64 *Samuels P B and Webster D R: The role of venous* endothelium in the inception of thrombosis, Ann Surg 136:422, 1952

65 Florey H W, Poole J C F, and Meek, G A: Endothelial cells and cement lines, J Pathol. Bact 77:625-636, 1959

66 Ohta G, Sasaki H, Fugitsugu M, Tanishima K, and Watanabe S: Heparin like substances in cement lines of vascular endothelium of guinea pigs, Proc Soc Exp Biol Med 109:298, 1962

67 Lazzarini Robertson, A. Jr: The uptake of labelled lipoproteins by isolated human and endothelial type cells. *in* Effect of Drugs on Synthesis and Mobilization of Lipid, edited by D Kritchevsky. New York, 1963 MacMillan Publishing Co Inc, pp 193-209

68 Hiebert L M, and Jaques L B: The observation of *heparin on endothelium after systemic injection.* Thromb Res 8:195, 1976.

69 Hiebert L M, and Jaques L B: Heparin uptake on endothelium. Artery 2:26, 1976

70 Mims, C A: The uptake of heparin by peritoneal macrophages. Aust J Exp Biol Med. 47:157, 1969

71 Glimelius B, Busch, C, and Hook, M: Binding of heparin on the surface of cultured human endothelial cells. Thromb Res 12:773, 1978

72 McGovern V J: Mast cells and their relationship to endothelial surfaces. J Pathol Bact 71:1, 1956

73 Zugibe F T: The demonstration of the individual acid mucopolysaccharides in human aortas, coronary and cerebral arteries. J Histochem Cytochem 10:448, 1962

74 Velican C: Topochemistry of acid carbohydrates in human aortic and coronary intima. J Atheroscler Res. 7:517, 196

75 Mann H M, and White H S: Anticoagulant activity of acidic mucopolysaccharides of the vascular wall. Fed Proc 22:619, 1961

76 Izuka K, and Murata K: Occurrence of heparin or its related acidic glucoseaminoglycan in human aortic tissue. Experientia 29:657, 1973

77 Buonassi, V: Enzymatic degradation of heparin related mucopolysaccharides from the surface of endothelial cell structures, Biochim Biophys Acta 385:1, 1975

78 McGovern V J: Reactions to injury of vascular endothelium with special reference to the problems of thrombosis. J Pathol. Bact 69:283, 1955

79 Srinivasan S, Aaron R, Chopra P S, Lucas T, and Sawyer P N: Effect of thrombotic and antithrombotic drugs on the surface charge characteristics of canine blood vessels. Surgery 64:827, 1968

80 Sawyer P N, Stanczewski, B, Pomerance A, Lucas T, Stover G, and Srinivassan S: Utility of anticoagulant drugs in vascular thrombosis. Electron microscopic and biophysical study. *Surgery 74:263, 1973*

81 Zilversmit D B, and Newman H A I: Does a metabolic barrier to circulating cholesterol protect the arterial wall? Circulation 33:7, 1966

82 Constantinides P, and Robinson M: Ultrastructural injury of arterial endothelium. Arch. Pathol 88:99, 1969

83 Majno G., Shea S M., and Leventhal, M Endothelial contraction induced by histamine type mediators, J Cell. Biol. 42 647 1969
84 Lazzarini Robertson A., Jr., and Khairallah, P A. Arterial endothelial permeability and vascular disease The "trap door" effect Exp Mol Pathol 18 241 1973
85 Shimamoto T Injury and repair in arterial tissue Angiology 25 682, 1974
86 Fabricant C G., Fabricant J., Litrento M M., and Minick C R Virus-induced atherosclerosis J Exp Med. 335 1978
87 Howard A. N., Patelski J., Bowyer D E., and Gresham G A Atherosclerosis induced in hypercholesterolaemic baboons by immunologic injury and the effects of intravenous polyunsaturated phosphatidyl choline Atherosclerosis 14 17 1971
88 Minick C R., Alonso D R., and Rankins L Role of immunologic arterial injury in atherogenesis Thromb Haemost. 39 304 1978
89 Jaques L. B The pharmacology of heparin and heparinoids Progr Med. Chem. 5 139 1967
90 Engelberg, H Probable physiologic functions of heparin Fed. Proc 36 70 1977
91 Engelberg H Heparin Physiology and pathobiology in Pathobiology Annuals vol. 8 ed. H L. Ioachim New York, 1978 Raven Press, p 85-104
92 Essien E M., Kinlough Rathbone R., Moore S., and Mustard J F The role of heparin on the inhibition of platelet adhesion to damaged arterial endothelial surface Thromb Diath. Haemorrhag 34 600 1975
93 Lagegren H., Larsson R., Olsson P., Radegran K., and Swedenborg J Depressed platelet adhesion as a characteristic of nonthrombogenic heparinized polymer surfaces Thromb Diath Haemorrhag 34 5?7 1975
94 Mustard J F Packham M A., Moore S and Hirsch, J Thrombosis and atherosclerosis, in Atherosclerosis III edited by G Schettler and A. Weizel, Berlin 1974 Springer Verlag pp 253-267
95 Wasteson A Glimelius B., Busch, C., Westermark, B., Heldin C H and Norbing, B Effect of a platelet endoglycosidase on cell surface associated heparan sulphate of human cultured endothelial and glial cells, Thromb Res 11 309 1977
96 Ross R Glomset J B Kariya B and Harker L. A platelet-dependent serum factor that stimulates the proliferation of arterial smooth muscle cells in vitro Proc Natl Acad Sci USA 71 1207 1974
97 Astrup T Albrechtsen O K and Classen M Thromboplastic and fibrinolytic activity of the human aorta Circ Res 7 [illegible] 19[illegible]
98 [illegible] E Hoak J C., and Warner E D Th[illegible] agulant and thrombogenic properties of human atheroma Circulation 36 [illegible] 1967
99 Bl[illegible] A [illegible] J [illegible] and Shearn S M Immun[illegible] alization of coagulation factors [illegible] Br J Haematol 25 2[illegible] 19[illegible]
100 Akbar H [illegible] Further evidence for the role of the [illegible] ease reaction caused by van [illegible] phosphatic platelet aggregation [illegible] 8 [illegible] 197[illegible]
101 Lou[illegible] induced [illegible] thrombin [illegible] 38 [illegible] 197[illegible]
102 Chen L B and [illegible] M [illegible] activity of blood components [illegible] Proc Natl Acad Sci USA 72
103 Nordoy A [illegible] Hoak J C Lipoprotein and the [illegible] human endothelial cells on platelet function Circ Res 43 [illegible] 1978
104 Essien E M., Cazenave J P., Moore S and Mustard J F Effect of heparin and thrombin on platelet adherence to the surface of rabbit aorta Thromb Res 13 69 1978
105 Czervionki, R L., Hoak, J C and Fry G L Effect of aspirin on thrombin induced adherence of platelets to cultured cells from the blood vessel wall, J Clin Invest 62 847 1978
106 Hoak, J C Platelet aggregation secondary to coronary obstruction Circulation 53(Supp 1) [illegible] 19[illegible]
107 Clowes A. W., and Karnofsky M J Suppression by heparin of injury induced myointimal thickening J Surg Res 24 479 1978
108 Philp R B., Francey I and Warren B A Comparison of antithrombotic activity of heparin ASA sulfinpyrazone and VK 744 in a rat model of arterial thrombosis Haemostasis 7 282 1978
109 Lazzarini Robertson A., Jr Effects of heparin on the uptake of lipids by isolated human and animal arterial endothelial cell types Angiology 12 525 1961
110 Reidy M A. and Bowyer D E Distortion of endothelial repair The effect of hypercholesterolemia on regeneration of aortic endothelium following injury by endotoxin Atherosclerosis 29 459 1978
111 Ross R., and Glomset L. Hyperlipidemia and atherosclerosis Science 193 1094 1977
112. Cullen C F., and Swank R L. Intravascular aggregation and adhesiveness of the blood elements associated with alimentary lipemia and injection of large molecular substances Circulation 9 335 1954
113 Williams, A V., Higginbotham A C and Knisely M H Increased blood cell agglutination following ingestion of fat a factor contributing to cardiac ischemia coronary insufficiency and anginal pain Angiology 8 29 1957
114 Brockner J., Amris C J., and Larsen V Fat infusion and blood coagulation Effect of various fat infusions and blood coagulability A comparative study Acta Chir Scand. (Supp) 343 48 196[illegible]
115 Lee K T Scott R F., Kim D M., and Thomas W A Clot strength and clot lysis in rats fed thrombogenic diets, Exp Mol Pathol 1 151 1962
116 Renaud S Kinlough R L and Mustard J F Relationship between platelet aggregation and the thrombotic tendency in rats fed hyperlipemic diets Lab Invest 22 339 1970
117 Nordoy A., Hamlin J T Chandler A. B and Newland H The influence of dietary fat on plasma and platelet lipids and ADP induced platelet thrombosis in the rat Scand J Haematol 5 4[illegible] 196[illegible]
118 Moolten S E., Jennings P B and Solon A Dietary fat and platelet adhesiveness in arteriosclerosis and diabetes Am J Cardiol 11 290 1963
119 Horlick L. Platelet adhesiveness in normal persons and subjects with atherosclerosis Effect of high fat meals and anticoagulants on the adhesiveness Am J Cardiol. 8 4[illegible] 1961
120 Steele P., and Rainwater J Effects of dietary and pharmacologic alteration of serum lipids on platelet survival times Circulation 58 [illegible] 197[illegible]
121 Getz G S Vesselinovitch D and Wissler R W A dynamic pathway of atherosclerosis Am J Med 46 6[illegible] 1969
122. Niinikowski J., Heughan C., and Hunt T K Oxygen tension in the aortic wall of normal rats Atherosclerosis 17 3[illegible] 1973
123 Heughan C., Niinikoski J and Hunt T K Oxygen

tensions in lesions of experimental atherosclerosis of rabbits Atherosclerosis 17 361 19 3
1?4 Astrup P Effects of hypoxia and of carbon monoxide exposures on experimental atherosclerosis Ann Intern Med 71 4?6 1969
1?5 Helin P and Lorenzen I Arteriosclerosis in rabbit aorta induced by systemic hypoxia Angiology 20 1 1969
1?6 Martin G J and Hueper W C Biochemical studies of atheromatous animals Proc Soc Exp Biol Med 49 452 1942.
1?7 Engelberg H and Kuhn R Studies of forearm arterio-venous oxygen differences in atherosclerotic patients before and after heparin Angiology 7 ?3 1956
128 Engelberg H Effect of heparin upon the total oxygen consumption of atherosclerotic patients Am J Med Sci 236 175 1958
1?9 Engelberg H The effect of heparin on oxyg n transport from blood to tissues Adv Exp Med Biol 52 ?99 19 5
130 Kuo P T and Joyner C R Jr Effect of heparin on lipemia induced angina pectoria J.A.M.A 613 ?27 195?
131 Kuo P T and Whereat A F Lipemia as a cause of arterial oxygen unsaturation and the effect of its control in patients with atherosclerosis Circulation 16 493 195?
13? Talbott G D and Frayser R Hyperlipidemia a cause of decreased oxygen saturation Nature 200 684 1963
133 Stutman L J Kniewaldt F H Doerr V, et al Effect of lipemia on arterial oxygen at high altitude J Appl Physiol 14 894 1959
134 Joyner C R Horwitz O and Williams, P G The effect of lipemia upon tissue oxygen tension in man Circulation 22 901 1960
135 Regan T J Timmis G Gray M Binak, K and Hellems, H K Myocardial oxygen consumption during exercise in fasting and lipemic subjects, J Clin Invest 40 6?4 1961
136 Sobotka H Monomolecular layers Medical Physics 2 550 950
13? Dervichian D G Progress in the Chemistry of Fats and Other Lipids New York 1954 Academic Press, Inc., p 214
138 Davidson D Eggleton I and Foggie P The diffusion of atmospheric gases through fats and oils Q J Exp Physiol 37 91 195?
139 Chisolm G M Gainer J L Stoner G E and Gainer J V Jr Oxygen diffusion and atherosclerosis Atherosclerosis 19 135 19 4
140 Gainer J L and Chisolm G M Oxygen diffusion and atherosclerosis Atherosclerosis 19 135 19 4
141 Barr D P Riess E M Eder H A Raymunt J and Aronson R Protein lipid relationships in human plasma II In atherosclerosis and related conditions. Am J Med 11 480 1951
142. Mjos O D High-density lipoprotein and coronary heart disease Scand J Clin Lab Invest 37 191 19?
143 Glueck C J Cartside P S Steiner P M Miller M Todhunter T Haat J Terrana M Follet R W and Kashyap M L Hyperalpha and hypobeta lipoproteinemia in octogenarian kindreds Atherosclerosis 27 38? 19?
144 Redgrave T G Formation of cholesteryl ester rich particulate lipid during metabolism of chylomicrons J Clin Invest 49 465 19 0
145 Bierman E L Eisenberg S Stein O and Stein Very low-density lipoprotein "remnant" particl Uptake by smooth muscle cells in culture Biochi Biophys Acta 329 163 19?3
146 Zilversmit D B A proposal linking atherogenesis the interaction of endothelial lipoprotein lipase wi triglyceride rich lipoproteins, Circ Res 33 633 19?
14? Holger Madsen T Reduction of heparin activity plasma globulins in pati nts with increased hepa resistance Acta Haematol 27 15? 1962.
148 Wolf P and Williams, S The serial thromboplas dilution test a presumptive test for hypercoagulabili Thromb Res 9 209 19?6
149 O Brien J R Antithrombin III and heparin clotti times in thrombosis and atherosclerosis. Thron Diath Haemorrhag 32 116 19?4
150 Okuno T, and Crockatt D Platelet factor 4 acti and thromboembolic episodes Am J Clin Path 67 351 19?
151 Cella G and Russo R Heparin neutralizing activi (HNA) and antithrombin III in coronary artery disea Thromb Haemost 38 696 19?
15? Lin C I Davis, J W, Yue K T N, and Philli P E Heparin neutralizing activity and corona artery disease AM. HEART J 94 25 19?7
153 Davis J W Defective platelet disaggregation ass ciated with occlusiv arterial diseases Angiolo 24 391 19?3.
154 McDonald L and Edgill M Action of heparin ischaemic heart disease Lancet 1 844 19?1
155 Wessler S Gitel, S N, Wan L S, and Pasternack S Estrogen-containing oral contraceptive agents basis for their thrombogenicity J.A.M.A 236 ?1 19?6.
156 Gitel S N Stephenson R C and Wessler S Th activated factor X - antithrombin III reaction rate measure of the increased thrombotic tend ncy induce by estrogen-containing oral contraceptives in rabbit Haemostasis 7 10 19?8
15? Muller Berghauf G Eckhardt T, and Kramer W The role of leukocytes and platelets in the precipitatio of fibrin in vivo mechanisms of the generation o microclots from soluble fibrin Thromb Res 8 ?5 19 6
158 Geertinger P and Sorensen H Complement and arteriosclerosis Atherosclerosis 18 65 19 3
159 Fust G Szocudy E Szekely J Nanai I and Gero S Studies on the occurrence of circulating immune complexes in vascular diseases Atherosclerosis 29 181 19?8
160 Ruddy S Gi li I and Austen K F The complement system of man N Engl J Med 287 489 545 592 64? 19?2.
161 Maroko P R Carpenter C B Chiariello M Fishbein M C, Radway P Knostman J D and Hale S L Reduction by cobra venom factor of myocardial necrosis after coronary artery occlusion J Clin Invest 61 661 19?8
162. Barkas, T Biologic activities of complement Biochem Soc Trans. 6 ?98 19 8
163 Rent R, Myhrman, R, Fied I B A and Gewurz H Potentiation of C1-esterase inhibitor activity by hepa rin Clin Exp Immunol 23 264 19 6
164 Weiler J M Yurt R W Fearon D T and Austen K F Modulation of the formation of the amplification convertase of compl ment C3b Bb by nati e and commercial h parin J Exp Med 147 409 19?8
165 Logue G L The effect of heparin on complem nt activation and ...

binuria (PNH) red cells, Blood 50 238 1978
166 Constantinides P., Szaz, G., and Harder F Retardation of atheromatosis and adrenal enlargement by heparin in the rabbit Arch. Pathol. 56 36 1953.
167 Horlick, L. and Duff L. G Heparin in experimental atherosclerosis in the rabbit Arch. Pathol 57 417 1954
168 Meng H C and Davis W S Effects of heparin on development of atherosclerosis and fatty liver Arch Pathol. 60 276 1955
169 Antonini, F M., Salvini L. and Minioni G Heparin protamine sulfate and experimental atherosclerosis Quoted in Chem. Abstracts 48 10209 1954
170 Franco A. Treatment of atherosclerosis with heparin Quoted in Chem Abstracts 50 14100 1956
171 Fodor J., Zemplenyi, T., Lodja Z. and Grafnetter D The effect of heparin and protamine sulfate on cholesterol atheromatosis in rabbits Quoted in Chem Abstracts 53 7438 1959
172. Myasnikov A. L. Influence of some factors on the development of experimental cholesterol atherosclerosis *Circulation* 17 99 1958
173 Constantinides P., Saunders P., and Wood A Effects of sulfated polysaccharides on pre-established atherosclerosis Arch. Pathol. 62 369 1956
174 Pilcher D B., and Barker W F Retardation of experimental atherosclerosis in endarterectomized arteries by the administration of heparin and dextran Am J Surg 120 270 1970
175 Grossman B J., Cifonelli, J A., and Ozoa A K Inhibition of atherosclerosis in cholesterol fed rabbits by a heparitin sulfate Atherosclerosis 13 103 1971
176 Moses C and Rhodes G L. The effect of heparin on cholesterol partition lipoproteins and atherosclerosis in experimental hypercholesterolemia Angiology 5 429 1954
177 Opdyke D F Rosenberg A., Silber R Ott W H., and Siegel H Effect of chronic injections of a heparin complex on aortic atherosclerosis in cholesterol fed chicken J Lab Clin. Med 45 270 1955
178 Roswell H C., Glynn M F., Mustard J F., and Murphy E A Effect of heparin on platelet economy in dog Am J Physiol. 213 915 1967
179 Pick R., Kakita C., and Katz L. N The effect of heparin and bishydroxycoumarin on cholesterol induced atherosclerosis in cockerels J Atherosclerosis Res 7 11 1967
180 Engelberg, H., Kuhn, R and Steinman M A controlled study of the effect of intermittent heparin therapy on the course of human coronary atherosclerosis Circulation 13 489 1956
181 Hughes, M L. Jr., Mortensen F., and Shourie L. Comparison of continuous long term heparin and oral anticoagulant therapy in patients with severe angina pectoris AM HEART J 65 615 1963
182. Bottiger L. E Carlson L. A Engstedt L., and Oro L. Long term heparin treatment in ischaemic heart disease Acta Med Scand 182 245 1967
183 Gertler M M., Leetma H E Koutrouby R J and Johnson E. D Long term use of mini-dose heparin in post myocardial infarction Adv Exp Med Biol 52 341 1975
184 Engelberg H and Kuhn R Further observation of long term intermittent heparin therapy in human coronary *atherosclerosis in Anticoagulant Therapy in* Ischemic Heart Disease edited by E S Nichol, New York, 1965 Grune & Stratton Inc pp 214 220
185 Griffith G C and Boggs R P Long term heparin therapy for ischemic heart disease Ibid., pp 134 137
186 Wagner R. T Long term heparin therapy in ischemic heart disease Ibid pp 284 289
187 Lovell R R H., Denborough M A Nestel P J and Goble A J Phenprocoumon and heparin after acute myocardial infarction Arch Intern Med. 113 967 1964
188 Schettler G Risikofaktoren beim herzinfarkt Deutsche Med Woch 97 1 19 2
189 Aviolι, L. V Heparin induced osteopenia an appraisal. Adv Exp Med Biol 52 375 19 5
190 Marciniak E., and Gockerman J P Heparin induced decrease in circulating antithrombin III Lancet 2 581 1977
191 Engelberg H Heparin and Atherosclerosis. Monographs on Atherosclerosis 8 19 8 edited by D Kritchevsky O J Pollak and H S Simms Basel 19 8 S Karger

American Heart Journal

Articles to appear in early issues

Duplicity in a Committee Report on Diet and Coronary Heart Disease
Kurt A Oster M.D Fairfield Conn

R wave amplitude changes during stress testing Comparison with ST segment depression and angiographic correlation
Lorenzo de Caprio Sergio Cuomo Paolo Bellotti Bruna Adamo Maurizio Postiglione Carlo Vigorito and Franco Rengo Naples Italy

The natural history of aortic stenosis in adults
Michael A Chizner M D David L. Pearle M.D and Antonio C deLeon Jr M.D Washington D C

Flail aortic valve leaflets M mode and two dimensional echocardiographic manifestations
Janine Krivokapich M.D John S Child M.D and David J Skorton M.D Los Angeles Calif

Relationship of plasma anti heparin activity and platelet survival time in coronary disease
Peter Steele M.D and Joseph Rainwater M.D Denver Colo

The effect of acebutolol on cardiac arrhythmias in patients with chronic coronary artery disease
Dieter Burckhardt M D and Ernst A Raeder M.D With the technical assistance of Elisabeth Blum Basel Switzerland

Clinical and morphological features of human hypertensive diabetic cardiomyopathy
Stephen M Factor M.D Takashi Minase M.D and Edmund H Sonnenblick M.D Bronx N Y

Technetium 99m stannous pyrophosphate myocardial scintigrams in pericardial disease
Harold G Olson M D Kenneth P Lyons M D Wilbert S Aronow M.D John Kuperus M.S Joan R Orlando M.D and Harris J Waters B S Long Beach and Irvine Calif

Intravenous quinidine pharmacokinetic properties and effects on left ventricular performance in humans
Hermann R Ochs M D Eberhard Grube M.D., David J Greenblatt M.D Elaine Woo M.D and Gunther Bodem M.D Boston Mass

Limitations of the standard transthoracic electrocardiogram in detecting subendocardial ischemia
R James Barnard Ph.D Gerald D Buckberg M.D and Henry W Duncan M.Sc Los Angeles Calif

Sialic acid depleted red cells following acute myocardial infarction
Victor A Hanson Jr M.D Stephen A Landaw M.D Ph.D Michael Flashner Ph D Stennis D Wax M.D and Watts R Webb M.D., Syracuse N Y

The abnormal heart rate response to a deep breath in borderline labile hypertension a sign of autonomic nervous system dysfunction
Louis C Johnston M D Chicago Ill.

Heparin has no direct action on pulmonary ·mboli.

Abbokinase (Urokinase for Injectio does!



PRE-INFUSION ANGIOGRAPH



2 HOUR POST INFUSION ANGIOGRAPH

Abbokinase®

(Urokinase for Injection)



250,000 I U per vial

- Abbokinase is not a foreign protein
- Abbokinase is non-antigenic
- Induced antibody formation is not seen in intradermal tests
- *Since patient is not sensitized by Abbokinase, therapy can be repeated whenever necessary*
- Urokinase neutralizing antibodies are not formed so resistance is not a factor
- Course of therapy is 12 hours and no dosage adjustment necessary

Abbokinase — the direct action thrombolytic agent for the management of acute massive pulmonary embolism

Due to a limited supply Abbokinase is stocked at strategically located hospitals throughout the country For the name of the hospital nearest to you please write Abbott Laboratories Dept 517 North Chicago, Illinois 60064

Please see following page for Brief Summary

9083308



Abbokinase®
Urokinase for Injection

Brief Summary

ABBOTT

90005008 R

ABBOKINASE (urokinase for injection) should only be used by physicians with wide experience in the management of thrombotic disease in hospitals where the recommended clinical and laboratory monitoring (see WARNINGS, PRECAUTIONS and DOSAGE AND ADMINISTRATION) can be performed.

When considering treatment with urokinase, the physician should carefully assess the overall clinical status and history of the patient. The hemostatic capability of the patient is more profoundly altered and bleeding more frequent with urokinase therapy than with heparin or oral coumarin anticoagulant therapy. When bleeding occurs it is also more severe and more difficult to manage. The potential risk of serious hemorrhage relative to such factors as age, physical condition and underlying bleeding tendency of the patient (as described under WARNINGS and PRECAUTIONS) should be weighed against the potential benefits of treating the patient with urokinase.

INDICATIONS
Pulmonary Embolism

ABB KINASE (rok nase for inject on) is ind cated in ad lts
for the lys s of acute mass e pulmonary emboli def ned as obstruct on or s gn f cant f lling de ects nvol g two or more lobar pu monary arteries or an equ valent amount of emboli n other essels
for the lys s of pulmonary embol accompanied by unstable hemody amics e fa lure to ma n ta n blood press re without s pportive measures
The diagnosis should be conf rmed by object e means p eferably p lmonary arte ography

Urok ase treatment should be nst tuted as soon as poss b a er onse of pulmo ary embolism and no la er than f ve days after onset Under these c rcumstances ang og aphic and hemodynam mea urements demonstrate a more rap d mp ovement dur ng the f rst 24 hours of therapy than w h heparin therapy (Table I) However t has not been establ shed that treatment w th urok nase decreases morb d ty or mortal ty when compared to heparin therapy alone

TABLE I

	UPET		USPET	
	Hepa n	12 Hour Urokinase	12 Hour Urok nase	24 Hour Uroki ase
Change in ang og aph c sever ty score ba ed on 4 point sys em	0 54	1 78	1 66	1 75
Decrease i rela ve pe centage perf s on defect on lung scans	8 3	24 1	20	29 2
Change pulmonary artery pressure (mm Hg)	−1 1	−6 2	−7 28	−7 53
Cha ge in card ac inde (l m m²)	−0 05	+0 02	+0 06	+0 30

Urok nase pulmonary embol sm trial
streptok nase pulmonary embol m trial
were ob a ned betwee 18 and 30 hours after the start of therapy After several days no d f erences between the results the heparin t eated pat e ts a d those rece v ng

CONTRAINDICATIONS — Beca se th ombolytic therapy creases the r sk of bleed ng urokinase contra ndicated in the follow g s tuations

1. S rgery w th ten days Live or kidney b opsy l mba punct e thoracentes s or paracentesis e te si or mult ple cutdowns should be cons d red s gical procedures
2. In raa erial d agnostic p oced e w th n ten days
3. Uice a ve wound
4. Recent tra ma with poss b lity nternal inj es
5. Visceral or intra r nial malignancy
6. Pregnancy and he f rs te days of he post partum pe iod
7. Ulc ra ve co s d verfic s or a act vely b eed ng lesion (or one w th a s fica t po e tial for bleed ng) of the gas oi es nal or ge tou nary tract
8. Severe hypertension
9. Acu e or ch onic renal c or al s fficienc
10. Uncon rolled hypocoag lable s e nc d ng one that may be ca sed by a coag lation factor deficiency thrombocy ope ia spont neous f b inolysis or ano her purpuric or hemor hagic d sorder
11. Chronic lung disease w h ca a ion g c ion s
12. Subacute bacterial endocar s or heuma ic a ia d s ase
13. Recent cerebral embol sm thrombosis or hemor hage T e me w th u ok nase s contra nd cated for at leas two mon hs a e b a embol sm n ombos s or hemorrhage beca se pa tients w h cerebral infarc ion ema a beed g t the farc ed tissue
14. Any other cond ion in w ic bleed ng m ors s g ica hazard or be particula ly e ffic lt to manage beca se of oca on

The cond ions lis ed above shou d no be ere a n ica ions R he the sk of hemorrhage must be weighed ca e a ns he cated benef s t okinase the apy n an individual pa ient and the benef s soc a ed w he se of ok ase should be compared to the benef ts and risks associated w m of he ny

WARNINGS
Bleeding

Activation of the fibrinolytic sys em with urok a e su in a more profound a tera tion of the hemostatic status of the pa ien h doe a oagulant the apy w h heparin or couma in a ents The aim of urokina e ther py the production of sufficient amounts of plasmin for the lys s ini a u depos s o fi in howe er fibrin deposits which provide hemostas s for mp i e ne e punctures are also des royed for lysis and bleeding from suc s me occur The possib l ty of bruising or hematoma forma ion especia w in amus ul e ion s h gh dur ing thrombolytic therapy Unnecessary handl ng he pa ient should be avoided Strict attention should be given to this sect on and the CONTRAINDICATIONS sec tion in order to minimize the risk of bleeding

Because of the fi n ia of hema oma forma ion m sc ar ns m be avoided d ing urokinase therapy as w th hepa ther py Bleed es of arte al e t ocedures mus be at lea t arterial invasive proce res must be limited be ts and ing the men w th urok nase Should an arterial punc ure be absolutely necessa y the femoral artery must be avoided and the radial or brac ial artery used It sho be done ly by a physicia e periences in such a procedure Pressure should be app eas 15 minutes a pressure dressing applied and the puncture s e checked f equen ident of bleed ng Ar ven punctures should be performed as caref lly and as infrequently as poss le If the bleed ng from a invasive s e is not serious treatment may be con inued w

Local measures (i.e. pressure) should be in t ated immediately

Spontaneous bleed ng from internal s tes (not acces ble for pressu e appl cation) may also occur The risk of spontaneous bleed ng is g eater n patients w th pre is ng hemos a ic defects e g pa e s w h h stor es sugge t ve of p o bleed ng problems w th or w thout demonstra e abnormal t es in platelet count, prothromb n time partial thromboplast n time or bleed ng time Such pat ents should be asse sed carefully before in t at ng t eatment w th urok nase

In add tion to its f br nolytic act on plasm n also degrades f br nogen Factor V Factor VIII and othe prote ns The products of plasmin degradation of f b nogen and f brin (FDP fdp) possess an ant coagulant effect Bleed g may be d ff cult to control beca se of this anticoagula t effect

Should serious spontaneous bleed g occur the nfusion of urok nase should be terminated im med ately and treatment instituted as descr bed under ADVERSE REACTIONS

Pred spos t on to Ce ebral Embol sm

Treatment w th u ok nase of pat ents w th atr al f br llat on or other cond tions in which there is poss ble risk of ce ebral embol sm may be hazardous because of the risk of bleed ng into the in farcted area

Use of Anticoagulants

Concurrent use of ant coagula s w h urok nase is not recommended and may be hazardous Before start ng urok nase n patients be ng trea ed w th hepar n the effects of hepa n should be allowed to d m n sh w th t me As a general rule a thromb n t me of less than twice the normal control val e i adequate for starting urok nase infus ons safely S m larly heparin should not be started follow ng urok nase therapy unt l the thromb n t me has returned to less than twice the *normal control alue*

Rethrombos s has been observed after term nation of u okinase treatment In order to m n mize th s r sk the use of intra enous hepar n followed by oral a ticoagulant therapy is considered a necessary adjunct followi g urok nase therapy (see DOSAGE AND ADMINISTRATION)

Use in Pregnancy

ee CONTRAINDICATIONS

Use in Ch ldren

Safety and effect veness of u ok na e therapy in ch ld en have not been establ hed the efore treatment of such pat ents is not recommended

PRECAUTIONS
Drug In era tions

Concurrent use of drugs that may alter platelet f nct on e g asp indomethacin and phenylbutazone should be avo ded The interaction of ABBOKINASE (urok nase for injection) w th other drugs has not been stud ed

Laboratory Monitoring

In pat ents who ha e rece ed hepar the thromb n t me should be measured prior to sta ting urokinase (See WARNINGS) S mila ly the thromb n t me should be mon tored follow ng ok nase therapy p or to inst tut ng hepa n (See DOSAGE AND ADMINISTRATION) D ng u ok nase ad m n strat on the levels of f br nogen pla m nogen Factor V and Factor VIII are usually substan tially d m n shed Concom ta tly the level of f b nlog n degradation products (FDP fdp) is in creased The comb nat on of reduced f brinogen a d creased FDP/fdp results in a prolonga ion of the thromb t m Wh le changes in any of these pa ameters may serve as conf rmation of the e istence of a lyt c state no adjustment of dosage should be made on the ba s of these test results

ADVERSE REACTIONS
Incidence and Management

Strict observance of the cont a nd cat ons wa ning and precaut ons to the use of urokinase is es sent al to m n m ze the nc de ce and seve ty of adve se effects

BLEEDING
Incidence

Where thrombolyt c age ts (st eptok nase and u ok nase) were used i the same cont olled cl ical t ial se e e bleed g (patients rece ng a transfusion of g eate than two u ts of blood) was seen n 4 and 6% respect ely Several fatal ties due to ce eb al hemor hage have occu red du ing u ok na e therapy

Less seve e spontaneous bleed g has been obser ed d ring urok nase trea ment a proximately tw ce the frequency as that occu ring dur g hepa n the apy Oozing of blood from s tes of percutaneous tra ma is freque t hence all n as e p ocedu es especia ly arterial punctures and int am scular injections m st be avo ded and intravenous punctures kept to a m nimum before and d ring treatme t w th urok nase

A modera decrease in hematocr t not accompa ied by cl ically detecta le bleed ng occurred in app ox ma ely one out of f ve pat e ts t eated w th urok nase

Management of Severe Bleeding

I case of se ious bleed ng u ok nase therapy m st be d scont nued If blood loss has been large packed red cells are indica ed Plasma vol me e panders (other t a Dex a) are indicated to replace blood volume d fic t If only whole blood is ava lable it may also be sed Although the use of am nocaproic acid (ACA, AMICAR) humans as a a tidote for rokinase has not bee docu me ted it may be considered if the hemorrhage is u respons ve to blood replacement (See WARNINGS)

ALLERGIC REACTIONS

Although u ok nase is a prote of human or g n, and in vitro tests w th the drug as well as in tradermal test i humans gave no evidence of induced ant body forma ion, the possibil y of se ious allergic reactions (ncluding anaphyla is) occu ng w th its use cannot be e luded Relat vely m ld allergic reactions e g bronchospasm and sk n rash were reported rarely

FEVER

Feb le episodes occurred in appro mately two to th ee out of 100 pa ie ts A cause and effect elations p has not been es a shed Sympto ma ic treatment is usua y su icien to allev te this comfort The use of acetaminophen ra her tha aspirin is recommended

DOSAGE AND ADMINISTRATION
Dosing

ABBOKINASE IS INTEN ED FOR INTRAVENOUS INFUSION ONLY

A pr ming dose of 2 000 I U /lb (4 400 I U /k) of ABBOKINASE is give as the Abbokinase-N saline admixture over a pe iod of te minu es This is followed by a con inuous infusion of 2 000 I U /lb/h (4 400 I U /kg/h) of ABBOKINASE (given as the Abbokinase-Normal Saline ad m) for 12 hours The total vol me of fluid a minis ered should not e ceed 200 ml

A m nister ABBOKINASE (ok nase for injec ion) by means of a constant infusion pump that is capa le of del vering a total vol me of 195 ml

Anticoagula ion After Terminating Urokinase Treatment

At the end of urokinase therapy t e ment w h hepa in by continuous i avenous infusion is recommended hepa in trea ment should not begin until the thrombin time has decreased to less than twice the normal con rol a ue See manufacturer s pres ibing information for proper use of

Fundamentals of clinical cardiology

Acute dissecting aneurysms of the aorta diagnosis and treatment—1979

Myron W Wheat Jr M D
Louisville Ky and St Petersburg Fla

The modern era of the diagnosis and treatment of acute dissecting aneurysms of the aorta was ushered in by DeBakey Cooley and Creech s report in 1955 The twenty four years since 1955 have seen tremendous strides in both the diagnosis and treatment of this devastating disease process The mortality rate has been decreased from over 90% at 3 months in untreated patients with acute dissecting aneurysms of the aorta[2] to 20 to 35% today utilizing current methods of diagnosis and treatment

The purpose of this report is to detail the diagnosis and treatment of acute dissecting aneurysms as it stands today 1979 The discussion does not include dissecting aneurysms of vessels other than the aorta and does not include dissecting aneurysms as the result of trauma produced by external forces or introduced at the time of catheterization or cardiopulmonary bypass

Incidence and pathogenesis

The incidence of occurrence of acute dissecting aneurysms of the aorta will vary some from one locality to another depending on the age and racial distribution of the population The acute dissecting aneurysm probably occurs at a rate of 5 to 10 per million population per year as a general average—or at least two to three times the incidence of the rupturing abdominal aortic aneurysm[3] Pate and colleagues[4] have estimated as high as 20 patients per million population in the Memphis area Clearly the acute dissecting aneurysm is not only the most common but the most lethal catastrophe that can involve the aorta

From th School of Medicine Department of Surgery Un rsity of Louisvill Louisvill Ky

Recei ed f public tion July 17 19 9

R print req ests Myron W Wheat Jr M D C rdiac Surgical Associates 747 Sixth A S St P tersburg Fla 33 01

Dissecting aneurysms occur with greatest frequency in the male population from 50 to 70 years of age In our own series 17% of the patients were over 70[5] Dissecting aneurysms are relatively rare in patients under 40 except in those with a familial predisposition[6] Marfan s syndrome[7, 8] or congenital heart disease such as coarctation of the aorta and/or bicuspid aortic valve[9, 10] As many as 50% of dissecting aneurysms seen in patients under the age of 40 may occur in pregnant women[11]

Hirst and associates and Pate and colleagues[4] believe there is no racial predilection for dissecting aneurysms However both Levinson and co workers[1] and Rider and colleagues[12] noted an increased incidence of dissecting aneurysms in the Negro In our own series[5] 60% of the patients were black whereas the hospital population was 30% black as was the surrounding community from which patients were drawn The higher incidence of dissecting aneurysms in the Negro may be related to their increased frequency of hypertension

Pathogenesis

Recent reports by Schlatmann and Becker[4, 15] have challenged previous concepts concerning changes in the media of the aorta and the relationship of those changes to acute aortic dissection

Previously medial degeneration—Erdheim s cystic medial necrosis loss of smooth muscle cells and elastic tissue in the media scarring fibrosis and hyalin like changes—was believed to be the specific basic underlying process in acute dissection The implication has been that the patient who suffered the acute dissecting process had an aorta with these degenerative medial changes, whereas the patients who did not have an

0002 8703/80/0303 3 + 15$01.50/0 © 1980 The C V Mosby Co

dissecting process possessed an aorta essentially normal i e without degenerative changes in the media of the thoracic aorta

Schlatmann and Becker[14] studied 100 normal aortas [14] The changes of cystic medial necrosis elastin fragmentation fibrosis and medionecrosis were tabulated as to distribution and extent There was a striking correlation with the normal aging process suggesting that medial degeneration probably is more generally present than previously suspected Their findings showed changes in the media that do correlate with the known frequency of the site of origin of acute dissecting aneurysms The changes of elastin fragmentation increased in severity with age but the changes were more pronounced in the ascending aorta and aortic arch than in the descending thoracic aorta Also the inner layers of the media were the most severely affected They speculate that these changes are related to trauma—the trauma being the forces transmitted by various hemodynamic events related to arterial blood flow

Fibrosis was shown to increase with age and again the most fibrosis was found in the inner layers of the media and correlated closely with the changes of medionecrosis

In their findings the thoracic segments were generally more involved than the abdominal segment and the ascending thoracic aorta was involved most frequently and to the severest degree As in the normal aging aorta within the aortic wall the inner layers were the most frequently involved

In summary the changes of medial degeneration are essentially the same as those of medionecrosis The changes tend to be more frequent and more extensive the older the patient and probably more extensive in patients with hypertension

It is apparent then that the same features of aortic medial degeneration are found in older persons and in hypertensive patients without dissection The difference from the aorta with dissection is quantitative rather than qualitative [1]

In a second study Schlatmann and Becker studied the aortic media from patients with dilated ascending aortas aortas with complete or incomplete dissection and aortas from patients with Marfan s syndrome They found only quantitative differences between the so called normal aging aorta and the obviously diseased aorta with aneurysms Schlatmann and Becker considered the changes in the media of the aorta that result in dissecting aneurysms to be the result of the processes of injury and repair initiated by hemodynamic events These changes they believe occur in varying degrees in all aortas and are not specifically related primarily to dissecting aneurysms of the aorta [14]

In one autopsy review of 34 cases with Marfan s syndrome dissecting aneurysm was present in 12 or 35% Medial necrosis of the aorta has also been found in most cases of dissecting aneurysms occurring during pregnancy

In fewer than 5% the changes are primarily those of syphilis or atherosclerosis Atherosclerosis does not appear to be a significant factor in the etiology of aortic dissections Atherosclerotic aneurysms are rare in the ascending aorta where about two thirds of dissecting aneurysms originate In the distal abdominal aorta where atherosclerotic changes are most pronounced and fusiform aneurysms related to atherosclerosis are common dissecting aneurysms are rare

Hypertension present in 87% of our series is the other common finding associated with the development of dissecting aneurysms However the incidence of dissecting aneurysms in the hypertensive population is not known

The most likely explanation of the pathogenesis of dissecting aneurysms given considerable added support by the work of Schlatmann and Becker [14] [1] is as follows

First consider the normal hemodynamic or hydrodynamic forces acting within the aorta with each heartbeat At an average of 70 heartbeats per minute this propagation of forces occurs just over 1 000 times a day or about 37 million times a year Viewing this situation externally in relation to the heart and thoracic aorta what occurs with each heartbeat? The heart which generates the force and motion is relatively fixed anteriorly by the sternum and rib cage and posteriorly by the vertebral column The heart ascending aorta and aortic arch are suspended much like the pendulum of a clock by the vessels to the head and upper extremities The thoracic aorta becomes fixed just distal to the left subclavian artery as it becomes rather firmly attached along the left side of the vertebral column

With each myocardial contraction the heart because of the rigid sternum and vertebral column moves predominately side to side producing a flexing in the ascending aorta and

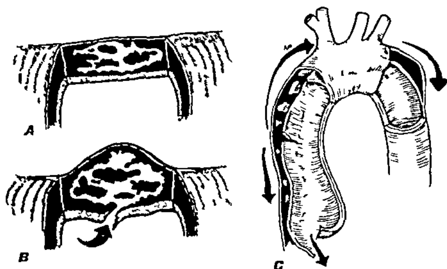


Fig 1 Diagrammatic representation of pathogenesis of dissecting aneurysms. *A* Degenerative changes in media of aorta sets the stage *B* Combination of forces produces intimal tear permitting arterial blood to enter weakened media *C* Resulting dissecting hematoma is propagated in one or both directions by the pulse wave produced by each myocardial contraction and the blood pressure

flexing just distal to the left subclavian artery where mobile aorta joins immobile aorta The extent and frequency of this flexing action can be simply documented by tracing the outline of the thoracic aorta during systole and diastole in the left anterior oblique projections of aortograms and then superimposing the two tracings Studies of 42 aortograms showed definite lateral movement of the ascending aorta in 95% Fifteen aortograms were evaluated for motion just distal to the left subclavian artery and 74% showed definite lateral motion[3]

Supportive evidence for the tendency of the aortic wall to be disrupted just distal to the left subclavian artery is available from studies of patients suffering deceleration accidents with traumatic rupture of the aorta Most of the disruptions occur in the area of the isthmus just distal to the left subclavian artery It is believed that the transverse tears occur in this area because it is the junction of mobile aortic arch with relatively fixed descending thoracic aorta Pressure from the left lung hilum and a cutting pressure from the recurrent nerve have also been implicated [9]

The explanation for the higher incidence of intimal tears in the ascending aorta rather than in the descending aorta or abdominal aorta is related to a number of factors

The hemodynamic events occurring inside the aorta with each cardiac systole probably have their greatest effect on the ascending aorta as shown by the most marked degenerative changes occurring with age in the ascending aorta[1, 5] The ascending aorta is also the area where the most external motion and flexion occur with cardiac systole The traumatic effect of the blood ejected from the heart against the ascending aortic wall may also play a role

As a result in certain patients as a consequence of many (if not all) of the factors—degeneration of the media recurring flexion of the aorta varying tensions applied to the aortic intima by the hemodynamic forces operating within the aorta—an intimal tear occurs 60 to 65% (Fig 1) in the ascending aorta 5 to 10% in the aortic arch and 30 to 35% in the first portion of the descending thoracic aorta The depth of penetration of the tear into the media and to some degree the distance of propagation of the subsequent dissecting hematoma is related to the extent of degeneration in each individual aortic media

Propagation of the dissecting hematoma

Following the intimal tear and the development of a dissecting hematoma a second set of forces becomes the most important These forces are those which primarily propagate or continue the dissecting hematoma and include blood viscosity blood pressure velocity (or shearing forces) turbulence and steepness of wave dP/dT *max*

— Experimental evidence indicates

most important forces propagating the dissecting hematoma are (1) the steepness of the pulse wave and (2) the blood pressure. There fore the forces that cause the dissection to *progress and to eventually rupture leading to the* death of the patient are originated by the heart and importantly related to peripheral arterial resistance afterload.

One major force responsible for continuation of the dissection derives from the pulsatile nature of *blood flow in large arteries. The reasoning is as* follows:

1 The aorta is markedly resistant to static pressure increases.

2 Static pressure provided no pressure gradient as driving forces to induce shear stresses or *other stresses on aortic tissue.*

3 Experimental models, e g Tygon tubing aorta with rubber cement intimas, *dissect* only when the flow is pulsatile and not when the flow is laminar or non turbulent. Experiments with dog aortas show the same relationship to *pulsatile flow as do the artificial aortas.*

4 Protection from aortic rupture in turkeys with dissecting aneurysms can be accomplished with propranolol, a beta adrenergic blocking agent, at a dose that does not affect aortic pressure but does alter the quality of pulsatile blood flow.

Experimental evidence supporting the importance of the blood pressure in the propagation of the dissecting hematoma comes from two principal sources: Carney and associates and Moran and associates. Carney's group showed that in their experimental model in dogs depression of myocardial contractility alone did not prevent progress of the dissection. However controlled hypotension plus depression of myocardial contractility completely inhibited progress of the dissection.

Moran and associates showed that in hypertensive dogs effective control of propagation of the experimental dissecting hematoma required reduction of the arterial pressure as well as reduction in the dP/dT.

Summary of pathogenesis

The pathogenesis of most dissecting aneurysms of the aorta can be looked upon as occurring as follows:

1 Medial degeneration in the wall of the thoracic aorta sets the stage by decreasing the cohesiveness of the layers of the aortic wall, particularly of the media itself (Fig 1A).

2 Repeated motion of the aorta related to the beating of the heart results in flexion stresses most marked in the ascending aorta and first portion of the descending thoracic aorta 60 to 100 times a minute, 37 million times a year.

3 Hydrodynamic forces in the bloodstream related to the pulse wave propagated by each cardiac cycle as well as the level of the systolic *blood pressure act upon the wall of the* aorta—most markedly the proximal aorta.

4 A combination of these factors eventually results in an intimal tear which leads to a hematoma dissecting into the media of the aortic wall for varying depths (Fig 1B). Hydrodynamic *forces in the bloodstream primarily related to the* steepness of the pulse wave dP/dT max as well as the blood pressure (Fig 1C) continue the propagation of the dissecting hematoma until rupture occurs either (1) back into the lumen of the aorta resulting in a spontaneous cure, a rare but *documented occurrence*, or more likely (2) rupture into the pericardium or pleural cavity leading to death within 30 days in most instances.

Diagnosis

Clinical picture Pain is the single most important and outstanding feature of the patient who presents with an acute dissecting aneurysm of the aorta. The pain is usually excruciating and may be described as sharp, knifelike, tearing or ripping in nature. The pain is usually the most severe the patient has ever experienced and is difficult, if not impossible, to relieve with opiates.

The pain most commonly is located in the anterior chest or in the back between the shoulder blades. The pain may begin in the chest, progress to the back and down along the spine. The pain may occasionally mimic the pain of angina pectoris with radiation into the shoulders and arms, rarely to the jaw or neck.

Two thirds to three fourths of the patients will have hypertension when seen or a history of hypertension in the past, not infrequently having recently discontinued their antihypertensive *medication.*

There are systolic murmurs over the precordium commonly, but the murmur of greatest importance is the murmur of aortic valve insufficiency, usually indicating a Type A (Fig 2)

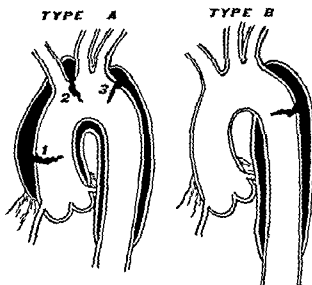


Fig 2 Classification of aortic dissections based upon the presence or absence of involvement of the ascending aorta (modified from Stanford [*]) The primary intimal tear in Type A dissections can be in the ascending aorta *(1)* and the transverse arch *(2)* or the descending aorta *(3)* Includes the DeBakey Types I and II The primary intimal tear in Type B dissections most commonly is distal to the origin of the left subclavian artery The dissecting hematoma does not involve the ascending aorta Includes DeBakey Type III Acute Type A dissections make up approximately 66% Type B make up 33%



Fig 3 Diagrammatic representation of the usual path of dissecting hematoma *(shaded area)* originating from an intimal tear in the ascending aorta

dissection with retrograde involvement of the aortic root—a particularly ominous sign

Murmurs over major branches of the aorta such as the carotid and subclavian arteries are secondary to partial occlusion of the vessel orifices by the dissecting hematoma There may be a significant difference in blood pressure between the two upper extremities the left subclavian being the most frequently involved

Even though the patient may appear to be in shock his blood pressure will usually be in the hypertensive range or he may show marked hypertension Occasional patients presenting in frank shock with a low blood pressure may demonstrate a rapid hypertensive response to the transfusion of only one or two units of blood

In any patient presenting with the onset of sudden severe pain involving the thorax abdomen or back the diagnosis of acute dissecting aneurysm of the aorta should be seriously considered Peripheral pulses that come and go disappear abruptly and acute neurological deficits are helpful but only present in 20 to 25% of cases

Once the diagnosis of acute dissecting aneurysm of the aorta is seriously entertained the next step is a chest roentgenogram followed by angiographic studies

Roentgenographic findings in dissecting aneurysms of the aorta

A chest roentgenogram which should be taken as soon as possible after admission as possible usually will show widening of the mediastinum However lack of mediastinal widening does not rule out dissecting aneurysm since this sign may be present in only 40 to 50% of cases Classically the mediastinum will bulge to the right with dissection of the ascending aorta and will show widening of the mediastinum on the left with involvement of the descending thoracic aorta Obliteration of the aortic knob with displacement of the trachea to the right are helpful signs [*] Previous chest roentgenograms if available are very useful for comparison

Mediastinal widening therefore is a highly

suggestive but non diagnostic sign of acute aortic dissection Neoplastic hemorrhagic[3] or inflammatory processes involving the mediastinum can produce similar widening Intramediastinal widening from leaking saccular aneurysms of the thoracic or upper abdominal aorta, can produce subadventitial dissecting hematomas These hematomas which do not involve the media of the aortic wall and therefore are not true dissecting aneurysms can result in false positive diagnoses even after aortography Calcium in the wall (intima) of the aorta with obvious widening beyond the calcium of at least 4 to 5 mm is usually considered diagnostic but only rarely present

Chest roentgenograms also may show pleural effusions most commonly on the left which are usually serous A serosanguineous pleural effusion does not necessarily mean that there is rupture or impending rupture of the aneurysm The adventitia can weep red blood cells from the dissecting hematoma producing a serosanguineous pleural effusion without an actual rupture of the wall of the aorta However a frankly bloody effusion is an obvious ominous sign indicating true leakage with impending pture

The typical path of the dissecting hematoma of the aorta is shown in Fig 3 When the dissection begins in the ascending aorta it is usually to the right and anterior just distal to the level of the coronary artery ostia As the hematoma advances into the arch it is posterior and superior In the descending thoracic aorta it is posterior and to the left There is a higher incidence of dissection into the left renal artery and the left ilio femoral system than into the right

The manifestations of dissecting aneurysms of the aorta on chest roentgenograms can be summarized as follows

1 Widening of the aortic arch

2 A change in configuration of the aorta on successive roentgenograms

3 Obliteration of the aortic knob with displacement of the trachea to the right

4 A localized hump on the aortic arch

5 Disparity in size of the ascending and descending thoracic aorta

6 Aortic wall thickening indicated by widening of the aortic shadow out de intimal calcification (rare)

Since chest roentgenograms are not diagnostic aortograms should be performed within 4 hours after admission to either confirm or rule out the diagnosis

Technique of aortography

The technique of aortography in patients suspected of having dissecting aneurysm of the aorta is as follows

The Seldinger percutaneous technique[7] using a femoral artery is followed using a pigtail or O Keefe catheter The catheter is passed over a J shaped guidewire with a 3 to 9 inch floppy tip The more tortuous the iliac artery and aorta the greater the need for a long flexible-tipped guide wire Careful manipulation together with the floppy J tipped guidewired catheter makes this a safe procedure This is virtually no danger of elevating a plaque and initiating a dissection

Hypaque M 75% is used as a contrast medium After a test hand injection a Viamonte Hobbs pressure injector is used for the definitive studies The amount used totals 130 to 150 ml for the two three or four separate injections The first injection is in the aortic root to look for the intimal tear and to evaluate the status of the aortic valve and the ostia of the coronary arteries Initially views are taken in the anteropo terior (AP) and the lateral projections with exposures taken alternately in each view The left anterior oblique position is used if the initial AP and lateral projections are not adequate Several minutes after the first injection the abdomen is fluoroscoped to obtain some idea of the location of the contrast material

After the first injection (we usually wait 15 or 20 minutes between injections) the films are evaluated and frequently the entire thoracic aorta is found to be adequately outlined The catheter is then withdrawn to just below the diaphragm where a second injection is made to determine the distal extent of the dissection and the degree of involvement of major abdominal branches of the aorta particularly the renal arteries

The diagnosis of dissecting aneurysm of the aorta can be made safely in most patients using the transfemoral Seldinger technique as described However occasionally the transaxillary approach will be necessary If neither the transfemoral or transaxillary approaches are feasible

or satisfactory the transseptal approach with left atrial angiography has been shown to be satisfactory for visualization of the aortic root[33]

The diagnosis by angiography is based on

1 Demonstration of two channels

a Linear radiolucency separating the two lumens

b Differences in flow with delayed opacification or delayed washout

2 True lumen only opacified

a Widening of outer extraluminal border of the aorta

b Narrowing of the true lumen with flattening of the side compressed by the dissecting hematoma

c Abnormal catheter recoil and position (only occasionally helpful)

3 In ascending aorta injection into false channel recognized by

a Demonstration of a blind end

b Failure to visualize the sinuses of Valsalva

c Flattening of the medial border of the opacified channel

d Delayed washout in the blind end

Shuford and associates[3] have pointed out some of the problems encountered in making the diagnosis of dissecting aneurysms of the aorta even by aortography In their series of 44 patients with suspected dissecting aneurysms the diagnosis was confirmed in only 23 by the demonstration of a narrowed true aortic lumen and a false channel In 11 cases there was no radiologic evidence of dissection In four patients with dissection the diagnosis was confused by faint false channel opacification unusual tearing of the intima and/or equal simultaneous opacification of both channels Layering of contrast material in the descending aorta in a patient with aortic valve insufficiency gave a false positive picture of a false channel In one patient widening of the mediastinum was secondary to rupture of a thoracoabdominal aneurysm in the mediastinum In the remaining four patients no definite diagnosis was made

Treatment

Ideally the aortogram should demonstrate the site of the intimal tear and the extent of the dissecting hematoma Once these two pieces of information are available the therapy most appropriate to that particular patient can be initiated Today excellent methods are available for definitive treatment of acute dissecting aneurysms of the aorta These methods involve the use of intensive drug therapy with or without surgical intervention depending on the type of dissecting aneurysm the age and over all condition of the patient and the hospital setting in which the treatment is to be carried out

Treatment modalities available

Intensive drug therapy Intensive drug therapy refers to the use of drugs or pharmacological agents to decrease the cardiac impulse (dP/dT max) and lower the systolic blood pressure as methods of treatment of the patient with an acute dissecting aneurysm of the aorta Today there are pharmacological agents available which can be used to dramatically lower the blood pressure with little effect on the heart itself In addition there are other agents which are available such as propranolol with a very selective effect on the heart producing a negative inotropic effect with little peripheral effect By the use of these agents singly or in combination one can achieve the desired effects of decreasing the steepness of the pulse wave[5] (dP/dT max) and at the same time dramatically lowering the blood pressure [5] thereby significantly altering both of the forces which must be diminished in order to stabilize or arrest the progression of the dissecting hematoma

Surgical therapy Surgical therapy[5,8] refers to definitive surgical intervention for the main dissecting process or its complications Such therapy involves (1) resection and graft replacement rather than fenestration procedures (2) occasional repair and end to end anastomosis of the aorta (3) resuspension or replacement of an insufficient aortic valve and (4) local procedures to restore flow in major branches of the aorta principally the iliac arteries The choice and use of these two principal modes of therapy either exclusively or in combination must take into account the facilities and surgical expertise in the hospital setting involved

Clinical basis The treatment of the patient with an acute dissecting aneurysm of the aorta initially with drugs followed by prompt diagnosis and then drugs alone or drugs plus appropriate and competent surgical intervention has been in

Table I Summary of 219 patients with acute dissecting aneurysms treated medically (108) or surgically (111)

Author ref	year reported	Ascending aorta (117 patients)				Descending aorta (102 patients)			
		Medical		Surgical		Medical		Surgical	
		Number	Survivors	Number	Survivors	Number	Survivors	Number	Survivors
Dailey[3]	1970	9	3	14	10	5	4	7	[illegible]
Attar[3]	1971	5	0	11	5	8	4	10	4
McFarland[19]	1972	6	2	–	–	10	8	–	–
Dalen	1974	9	2	22	17	6	6	8	2
Strong[*]	1974	15	3	9	5	19	15	12	[illegible]
Bolooki	1979	2	2	15	13	14	13	3	2
TOTAL		46	12	71	50	62	50	40	20
MORTALITY		74%		30%		20%		50%	

Fourteen patients were initially treated with drugs but in eight the progress of dissection was not controlled which is an indication for surgical intervention These eight patients are shown as surgical since definitive surgical therapy intervened appropriately

use for more than 15 years The therapeutic effectiveness of this approach is well documented by data from a number of different centers (Table I)

Table I is a collection of the results from six separate centers reported since 1970[35-40] In each center listed an attempt was made to use both intensive drug therapy as well as surgical therapy the treatment of patients with acute dissecting eurysms of the aorta Results reported from groups using only one method or the other, or where the treatment was incomplete or not standardized are not included

The results (Table I) show convincingly that all patients with acute dissecting aneurysms should be stabilized with intensive drug therapy accurately diagnosed, and then treated appropriately with drugs alone or with drugs plus definitive surgery for localized life threatening complications of the dissecting process

Seventy one patients with acute dissecting aneurysms involving the ascending aorta (Type A) (Fig 2) were stabilized diagnosed and treated surgically with an overall mortality rate of 30% This compares to a mortality rate of 74% when surgical intervention was not used On the other hand in the patient with the acute Type B dissection drug therapy alone yielded a survival rate of 80% compared to 50% when surgical intervention was added

Recently Shumway s group reported their experience with 73 patients with acute dissections (less than 2 weeks old) seen over the past 16 years and treated primarily with surgery * Fifty three were Type A and 20 were Type B The operative mortality rate was 34% for A and 45% for B Patients with acute Type A dissections had an increased operative mortality rate if hypertension was present as it was in 51%

Major complications that could be directly attributed to the dissecting process also significantly influenced the surgical result The complications of pleural rupture aortic regurgitation pericardial rupture cardiac tamponade loss of peripheral pulse(s), loss of arteriographic renal and/or visceral perfusion, cerebrovascular accident, shock anuria and arterial thromboembolism paraplegia and acute myocardial infarction all increased the operative mortality rate The operative mortality rate for patients with an acute Type A dissection was 14% without any of the above complications as compared to 36% with complications acute Type B mortality rate was 11% without versus 73% with The three most significant complicating factors were cerebrovascular accident, loss of arteriographic vessel or renal perfusion and paraplegia

Shumway s experience is important because it is a very detailed account of a large consecutive series of acute dissecting aneurysms treated surgically by competent cardiovascular surgeons The experience documents that the acute dissecting

Presented at the th Annual Meeting The American Association for Thoracic Surgery April 30 Ma 1979 Boston Massachusetts

Table II Operative mortality rate and sample size in selected series since 1970 the data in the original reports have been reclassified when necessary to correspond with the Stanford Type A and B classification criteria*

			Acute							
			Type A				*Type B*			
			Surgical		*Medical*		*Surgical*		*Medical*	
Series	*Reference*	*Year*	*No*	*%*	*No*	*%*	*No*	*%*	*No*	*%*
Maryland	3,	1971	10	60%	5	100%	10	50%	8	50%
UCLA	42	19,2	9	89%	—	—	2	50%	—	—
Yale	40	1974	9	45%	15	60%	12	42%	19	21%
PBBH†	39	19?4	2?	23%	9	78%	8	75%	6	0%‡
SUNY Upstate	43	19,5	3	100%	?	50%	1	0%	2	0%
THI Houston§	44	1975	—	—	—	—	49∥	25%	—	—
Alabama	45	1976	17	24%	17	88%	11	36%	22	3?%
THI Houston§	46	19 6	24	21%	—	—	—	—	—	—
Memphis	4	1976	8	63%	25	80%	14	43%	1	100%
THI Houston§	47	19 7	51	18%	—	—	—	—	—	—
Virginia	48	19,9	26	?3%	3	100%	14	36%	9	6?%
Average			1,9	38%	,6	83%	1?1	36%	67	?2%
Present study		19 9	53	34%	—	—	20	45%	—	—

This table is excerpted from Table IX ref 35 with the author s permission
†Peter Bent Brigham Hosp tal (3% of 45 total cases were acute)
‡*All acute Type B patients failing medical therapy crossed over to surgery*
§Texas H art Institute some patients in reference 4 are included in reference 46
∥Six of 12 deaths had retrograde extensions of their dissections in perioperati e period

aneurysm continues to be a difficult surgical problem with an over all surgical mortality rate of 34% for patients with acute Type A dissections and 45% for those with Acute Type B dissections During the most recent 5 years these have been reduced to 27% for Type A and 20% for Type B

Table II reproduced in part* from Shumway s report is a compilation of 11 reported series of acute dissecting aneurysms treated since 1970 Series are included that used both medical and surgical therapy surgical therapy only and regardless of whether any attempt at a standard ized approach to therapy was used The similarity of results when compared with Table I where only those series where an attempt at a standard ized approach to treatment using both medical and surgical therapy are shown is striking

For acute Type A aneurysms the mortality rate for surgical therapy was 30% in Table I and 38% in Table II medical therapy 74% in Table I 83% in Table II Type B surgical therapy was 50% in Table I and 36% in Table II (45% Shumway) medical therapy 20% in Table I 22% in Table II

The over all results are remarkably similar and add overwhelming support to the proposed plan of therapy for acute dissecting aneurysms of the aorta

A recent report from the University of Miami ' demonstrates further the results that can be obtained by the proper blending of the two available methods of therapy A protocol was established prospectively and adhered to in all but *five patients*

Over a five year period 1972 to 1977 32 patients with the diagnosis of acute aortic dissec tion confirmed by aortography were admitted to the cardiovascular surgery intensive care unit All patients with Type A dissections were operated upon after stabilization with drugs and diagnosis by aortography for emergency surgical repair Type B dissections were treated with drugs alone Two patients with Type A acute dissections were not operated upon—both patients refused and in

*Only th d t concern g cut dissect ons are reproduced

Table III Summary of treatment results of 32 patients with acute dissecting aneurysms of the aorta treated 1972 1977 University of Miami Florida[a]

Site of intimal tear	No	Emergency surgery (no)	Operative death (%)	Medical therapy		Delayed repair		Late death (no)
				Total	Death	Total	Death	
Ascending aorta Type A	15	13	2 (15%)	2	0	–	–	2 1 3 mos. Stroke 1-4½ yrs Marfans
Descending aorta Type B	17	3	1	14	1 (7%)	4	0	0

both there was no aortic valve insufficiency and rapid control of hypertension was achieved Three patients with Type B dissections were operated upon because of enlarging hematoma small true lumen of descending thoracic aorta and inability to control hypertension

The results of treatment of the 32 patients with acute dissection are summarized in Table III There was a total of 16 patients subjected to urgent surgical repair with three deaths—19% Sixteen patients were treated with drugs alone with one death—6% Long term survival (3 years) for patients with Type A dissection treated with drugs plus surgical repair and then long term drug management was 77% (14 of 18) and for patients with Type B dissection treated with drugs alone—91% (20 of 22)

Based on the best available experimental and clinical evidence at the present time the most rational form of therapy for patients with acute dissecting aneurysms is as follows

Treatment in a community hospital In the community hospital (without 24 hour expertise available for definitive aortography and without an experienced cardiovascular surgical team) the following treatment should be instituted as soon as the diagnosis of an acute dissecting aneurysm is suspected

If the patient is hypertensive and in pain initiate appropriate drug therapy to reduce the blood pressure and control the pain As soon as the patient's condition is stable and the pain relieved usually within 1 to 2 hours move the patient (plus chest roentgenograms) at once by ambulance to the nearest medical center where definitive angiographic and cardiovascular surgical expertise are available

If the patient is not hypertensive but is in pain reduce systolic blood pressure 20 to 40 mm Hg carefully observing urine output stabilize at a pain free level if possible and then transfer the patient

Treatment in a medical center A medical center is defined as having definitive angiographic and cardiovascular surgical expertise available 24 hours a day Patients suspected of having acute dissecting aneurysms of the aorta should be placed in a *cardiovascular surgical* intensive care unit where they can be monitored carefully on a minute to minute basis Other cardiovascular catastrophes such as acute myocardial infarction or cerebrovascular hemorrhage must be ruled out by appropriate studies and consultations

It is mandatory that these patients be managed and followed on a *cardiovascular surgical service* The cardiovascular surgeon must make the decision as to which type of therapy or combination of therapies should be used All patients should be treated with drugs initially but certain patients will need to be taken to surgery promptly and the surgeon is the only one who can make the decision as to when it is appropriate to supplement drug therapy with definitive surgical intervention

In the cardiovascular surgical intensive care unit

1 Monitor ECG blood pressure pulmonary artery wedge pressure and pulmonary artery pressure via a Swan Ganz type catheter and insert a Foley catheter to monitor the urinary output

2 Reduce systolic blood pressure to 100 to 120 mm Hg (if appropriate) Use trimethaphan (Table IV) (Arfonad—Table) 1 to 2 mg/ml as intravenous drip acutely and if necessary for 24 to 48 hours with a flow rate to maintain the desired blood pressure Keep the head of the bed elevated 30 to 45 degrees to enhance the orthostatic effect of the drug

Sodium nitroprusside (Table IV) should be used only if the patient becomes tachyphylactic to the trimethaphan or does not respond Nitroprusside although a potent hypotensive agent has been shown in the laboratory to definitely

Table IV Drugs used in treating dissecting aneurysms of the aorta

Drug	Mechanism of action	Total effect
Trimethaphan (Arfonad)	Ganglionic blockade direct relaxing effect on vascular smooth muscle histamine release	Decreases myocardial contractility lowers peripheral resistance produced ileus bladder distention pupil dilation
Propranolol (Inderal)	Specifically blocks beta adrenergic stimulation at end-organ receptor (blood vessels heart)	Bradycardia (reduces cardiac output) increases peripheral resistance mild hypotensive effect
Alpha m thyldopa (Aldomet)	Metabolized to alpha methylnorepinephrine a weak neurotransmitter and pressor agent which replaces the more potent norepinephrine at nerve terminal other unknown mechanisms	Sedation little depression reduces peripheral resistance sli ht bradycardia drug fever abnormal liver function hepatitis
Thiazides (Diuril Hydrodiuril)	Decreased tubular reabsorption of Cl and Na some K is lost results in salt and/or extracellular fluid volume depletion with a possible direct cardiovascular effect	Decrease in blood pressure
Reserpine	Depletes all catecholamines from all tissue stores neurotransmitter (norepinephrine) release diminished after nerve stimulation	Decreases myocardial contractility sedation depression bradycardia (reduces cardiac output) reduces peripheral resistance stimulates gastric secretion
Guanethidine (Ismelin)	Selectively depletes catecholamines from postganglionic nerve terminals particularly in the heart gastrointestinal tract blood vessels but not the central nervous system	Postural hypotension diarrhea bradycardia (reduces cardiac output) decreases peripheral resistance no effect on central nervous system
Sodium nitroprusside (Nipride)	Selectively relaxes vascular smooth muscle	Rapidly lowers blood pressure lowers peripheral resi tance reduces cardiac output indirectly by decreasing preload (venous return) produces definite increase in myocardial contractility (dP/dT max)

increase dP/dT If nitroprusside is to be used pretreatment of the patient with either propranolol methyldopa or reserpine should be carried out This pretreatment with a sympathetic blocking agent will diminish the initial reflex adrenergic stimulating effect of nitroprusside which is a result of the direct relaxation of the peripheral vascular bed

The blood pressure response to trimethaphan is usually rapid and must be regulated carefully Renal complications as a rule occur only with a profound lowering of the blood pressure for a significant period of time and can be virtually eliminated by careful monitoring of the patient Usually when the blood pressure is appropriately lowered the patient s pain is dramatically relieved

The severe pain that patients experience with an acute dissecting aneurysm is most likely secondary to stretch of the adventitia due to the expansion accompanying propagation of the dissecting hematoma Relief of the pain by decreasing the forces which are responsible for propagating the dissection i e dP/dT max blood pressure etc indicates arrest and stabilization of the dissecting process Therefore initial as well as continued relief of pain is probably the single most important clinical sign in the management of these patients

Once the patient s blood pressure (and cardiac impulse dP/dT max) and pain are brought under control indicating arrest of the progress of the dissecting hematoma and therefore arrest of the threat of rupture with death of the patient and the patient s condition is stabilized the diagnosis must be confirmed or ruled out by aortography

If the aortogram confirms the diagnosis of an acute dissecting aneurysm then the treatment depends on several factors The type of the dissecting aneurysm (Fig 2) (Type A indicating that the dissecting process involves the ascending aorta or Type B indicating that the dissecting

process involves the descending thoracic aorta *without* involvement of the ascending aorta) and the age and condition of the patient determine the specific therapy The differentiating point of most importance is involvement or lack of involvement of the *ascending thoracic aorta*[35,36]

Type A Acute—the ascending aorta is involved by the dissecting process

The intimal tear is usually in the ascending aorta or transverse aortic arch with the *ascending aorta* involved by the dissecting hematoma The important factor is *involvement of the ascending aorta* by the dissecting hematoma with the threat of retrograde dissection and fatal pericardial tamponade This type of acute dissecting aneurysm can be corrected surgically today with a mortality rate in the range of 15 to 30%[35, 1] Therefore the patient with an acute Type A dissecting aneurysm who is otherwise a good surgical risk and under control with suitable drug therapy should be taken to the operating room promptly and appropriate corrective surgery should be performed as soon as the patient s condition can be stabilized with drug therapy and the diagnosis has been confirmed by aortography

The improvement of surgical results in those patients with this particularly treacherous lesion is due in part to the use of drugs to stabilize the patient s condition arresting the progress of the dissecting hematoma and taking the patient to surgery on a prompt urgent basis rather than as an unstabilized surgical emergency The improvement in cardiovascular surgical skills and the management of cardiopulmonary bypass over the past 15 years have been the other significant factors in improving results in the patients with these difficult problems

Type B Acute—the dissecting hematoma is distal to the left subclavian artery

This type of dissecting aneurysm for therapeutic purposes also includes dissections originating in the transverse aortic arch but *without* involvement of the ascending aorta—the key is lack of involvement of the ascending aorta by the dissecting process All patients with Type B acute dissecting aneurysms should be treated initially with drug therapy

After the aortogram establishing the diagnosis of an acute Type B dissection the patient should be returned to the cardiac surgical intensive care unit

1 Continue to regulate the blood pressure with trimethaphan

2 Administer alpha methyldopa 250 to 500 mg intramuscularly or intravenously every 4 to 6 hours (Table IV)

3 Continue to monitor ECG blood pressure peripheral pulses urinary output and examine stools for blood

4 Take daily chest roentgenograms to check for progressive mediastinal widening or changes in thoracic aortic contour and for pleural fluid

If the patient s condition stabilizes the patient is not in pain and there is no evidence of progress of the dissection drug therapy should be continued into the chronic long term phase

Surgical intervention for the Type B acute dissecting aneurysm is indicated when any of the following occurs

1 Progress of the dissecting hematoma as shown by (a) significant increase in the size of the dissecting hematoma while the patient is receiving maximal intensive drug therapy (b) appearance of or changing murmurs over arterial branches of the aorta or the aortic valve area indicating continued progress of the dissecting hematoma with involvement of the ascending aorta (c) signs of compromise or occlusion of a major branch of the aorta such as deepening coma stroke painful cool extremity marked decrease in or cessation of urinary output

2 Impending rupture of the dissecting hematoma as evidenced by (a) acute saccular aneurysm by aortography (b) significant increase in size of the aneurysm within hours (c) blood in the pleural space or pericardium (d) lack of ability to control pain with intensive drug therapy

3 Inability to bring blood pressure or pain or both under control within 4 hours after start of intensive drug therapy

Summary of treatment indications for intensive drug therapy

1 Drug therapy is the initial treatment of choice in all patients with acute dissecting aneurysms

2 Type B dissecting aneurysm no involvement of the ascending aorta by the dissecting process

3 The site of the intimal tear cannot be iden

tified on the aortogram and there is no involvement of the ascending aorta

4 The site of origin is in the transverse arch without extension of dissecting hematoma into the ascending aorta

5 Patients who are poor surgical risks in general

6 Stable chronic aneurysms onset more than 14 days earlier

7 Community hospital that lacks facilities for definitive aortography and experienced cardiovascular surgical team

8 Failure of opacification of the false channel

Summary of treatment indications for definitive surgical therapy

1 Type A dissecting aneurysm the ascending aorta is involved by the dissecting hematoma

2 Aortic valve insufficiency secondary to dissecting aneurysm (means ascending aorta is involved also!)

3 Localized or impending rupture

4 Progress of the dissecting hematoma while receiving maximal drug therapy

5 Compromise or occlusion of a major branch of the aorta

6 Acute saccular aneurysm

7 Blood in pleural space or pericardium or both

8 Inability to relieve and control pain

9 Inability to bring blood pressure and cardiac impulse under control within 4 hours

Follow up therapy

The management and follow up after the acute phase is the same whether drugs alone or drugs plus surgery have been used Drug therapy should be continued in patients who have undergone surgical correction for dissecting aneurysms The underlying pathologic process aortic medial degeneration is still present and will tend to progress[5, 16, 1] These patients are prone to have either a localized redissection or to sustain a second separate dissection of the aorta

As the patient s clinical status stabilizes and the administration of intravenous agents—trimethaphan or sodium nitroprusside—is discontinued the patient should be transferred to routine hospital floor care for progressive ambulation and final regulation of drugs During the first week of therapy in the hospital daily chest roentgenograms to check for progressive mediastinal widening or changes in thoracic aortic contour and pleural fluid are indicated

Orthostatic hypotension is frequently observed at this time and the drug dosages must be regulated to maintain the desired hemodynamic effects while permitting relatively normal activity I prefer to discharge these patients with a systolic blood pressure no higher than 130 mm Hg supine and a minimal oral dosage of 60 mg of propranolol or 500 mg of alpha methyldopa per day Reserpine up to 0 5 mg /day and guanethidine are still used occasionally The addition of one of the thiazide diuretics is also frequently useful (Table IV) The physician should not hesitate to combine several drugs in seeking the best combination producing the desired blood pressure and inotropic control with the fewest undesirable side effects in a particular patient (Table IV)

Follow up care consists of a first visit to the physician at a one month interval and then regular visits at three month intervals At each visit these patients are checked for a history of pain the presence or absence of peripheral pulses and murmurs the level of blood pressure murmurs in the aortic area particularly that of aortic valve insufficiency prosthetic valve sounds if the aortic valve has been replaced and the status of the chest roentgenograms

The chest roentgenograms are important for continued evaluation of the size of the aneurysm or the area of graft insertion or both or of the aortic anastomosis Localized saccular aneurysms can develop in as many as 14 to 25%[1, 41] of patients with Type B aneurysms in the chronic follow up phase When saccular aneurysms are suspected they should be documented by aortograms and promptly replaced with a tubular prosthesis

If circumstances permit it is worthwhile to teach a member of the family to check and record the patient s blood pressure on a daily basis The blood pressure check should be performed at the same time each day with the patient both supine and standing A daily record available for review at each visit is helpful for blood pressure regulation

I do not know of a single instance of a patient with an acute dissecting aneurysm treated with drugs and followed continuously in the manner outlined above in whom the aneurysm has ruptured abruptly In my experience impending

trouble in the follow up period has always been evident on the basis of (1) signs and symptoms of progressive aortic valve insufficiency (2) chest or back pain or (3) enlargement of a saccular area of the aneurysm visible on chest roentgenogram These findings have allowed sufficient time for appropriate aortography followed by elective surgical therapy when indicated

Prognosis

Physicians using the approach to the treatment of acute dissecting aneurysms described here should achieve an over all hospital survival rate of at least 70 to 80% depending upon the patient population In those patients with acute dissecting aneurysms of the aorta treated with drug therapy alone one should anticipate the development of localized saccular aneurysms in 14 to 20% of patients and progressive aortic valve insufficiency ultimately requiring aortic valve replacement in about 10% following discharge from the hospital Those patients whose dissecting hematoma does not opacify an initial aortography and who are or should be treated with drugs alone can be expected to do well without the development of saccular aneurysms In those patients with aneurysms involving the ascending aorta Type A whose ascending aorta is either anastomosed or replaced with or without aortic valve replacement the results are good for at least 5 to 7 years

REFERENCES

1 DeBakey M E Cooley D A and Creech O Jr Surgical considerations of dissecting aneurysm of the aorta Ann Surg 142 586 1955
2 Hirst A E Johns V J and Kime S W Dissecting aneurysm of the aorta a review of 505 cases Medicine 37 217 1958
3 Wheat M W Jr and Palmer R F Dissecting aneurysm of the aorta Monograph Current Problems in Surgery
4 Pate J W Richardson R L and Eastridge Acute aortic dissection June 19
5 Wheat M W Jr Dissecting aneurysms of the aorta J Thorac Surg 58 344 1969
6 Hanley W B and Jones N Familial dissecting aortic aneurysm cases within two generations Br H 29
7 Sinclair R J Turner R W Marfan syndrome Q J Med 29
8 McKusick V A Marfan's syndrome a heritable disorder of connective tissue Circulation 11 321 1955
9 Strauss R C and McAdam dissecting aneurysm in childhood J Pediatr 76
10 Edwards W D Leaf D Dissecting aortic aneurysm associated with congenital bicuspid aortic valve Circulation 57
11 Mandel W Evans E W and Walsford R L Dissecting aortic aneurysm during pregnancy N Engl J Med 251 1059 1954
12 Levinson D C Edmeades D T and Griffith G C Dissecting aneurysm of the aorta its clinical electrocardiographic and laboratory features a report of 58 autopsied cases Circulation 1 360 1950
13 Rider J A Chriss J W and Herrmann G R Dissecting aneurysms of aorta a ten year study Texas State J Med 46 311 1950
14 Schlatmann T J M and Becker A E Histologic changes in the normal aging aorta implications for dissecting aortic aneurysm Am J Cardiol 39 13 1977
15 Schlatmann T J M and Becker A E Pathogenesis of dissecting aneurysm of aorta Comparative histopathologic study of significance of medial changes Am J Cardiol 39 21 1977
16 Atta A C and Hoch J Marfan's syndrome and dissecting aneurysm of aorta Arch Intern Med 108 781 1961
17 Lundevall J The mechanism of traumatic rupture of the aorta Acta Pathol Microbiol Scand 62 34 1964
18 Pate J W Butterick O D and Richardson R L Traumatic rupture of the thoracic aorta JAMA 203 1022 1968
19 Rittenhouse E A et al Traumatic rupture of the thoracic aorta a review of the literature and a report of five cases with attention to special problems in early surgical management Ann Surg 170 87 1969
20 Prokop E K Wheat M W Jr and Palmer R F Hydrodynamic forces in dissecting aneurysms Circ Res 27 121 1970
21 Carney W I Jr Rheinlander H F and Cleveland R J Control of acute aortic dissection Surgery 78 114 1975
22 Moran J F Derkac W M and Conkle D M Pharmacologic control of acute dissection in hypertensive dogs Surg Forum XXIX 231 1978
23 Shekelton J Dissections of aneurism Dublin Hosp Rep 3 231 1822
24 Conston A S Healed dissecting aneurysm Arch Pathol 48 309 1949
25 Morgan Jones A and Langley F A Chronic dissecting aneurysms Br Heart J 8 191 1946
26 Shennan T Completely healed dissecting aneurysm of the aorta with obliteration of the sac J Pathol 35 161 1932
27 Cassidy M and Pinniger J Healed dissecting aneurysm Br Heart J 7 8 130 1946
28 Young J R Kramer J and Humphries A W The ischemic leg a clue to dissecting aneurysm Cardiovasc Clinics vol Issue 1 01 19
29 Itzchak Y Rosenthal T Adar R Rubinstein Z J Lieberman Y and Deutsch V Dissecting aneurysm of thoracic aorta reappraisal of radiologic diagnosis J Roentgenol Rad Ther Nucl Med 125 1975
30 Berry F Carpenter P C Fulton R F and Danielson C K Mediastinal hemorrhage from parathyroid adenoma simulating dissecting aneurysm Arch Surg 108 40 1974
31 Eyler W R and Clark M D Dissecting aneurysms of the aorta roentgen manifestations including a comparison with other types of aneurysm Radiology 85 104 1965
32 Seldinger S I Catheter replacement of the needle in percutaneous arteriography a new technique Acta Radiol 39 368 1953
33 Kronzon I Deutsch F C LeFleur R and Clawman E Diagnosis of dissecting aortic aneurysm by left atrial

angiography Am J Roentgenol Rad Ther Nucl Med 124 458 1975
34 Shuford W H Sybers, R G and Weens H S Problems in the aortographic diagnosis of dissecting aneurysms of the aorta N Engl J Med 280 225 1969
35 Miller D C Stinson E B Oyer P E Rossiter S J Reitz B A Griepp R. B and Shumway N E The operative treatment of aortic dissections experience with 125 patients over a sixteen year period J Thorac Cardiovasc Surg 1979 (In press)
36 Daily P O., Trueblood H W., Stinson E B Wuerflein R. D and Shumway N E Management of acute aortic dissections, Ann Thorac Surg 10 237 1970
37 Attar S Fardin R Ayella R and McLaughlin J S Medical vs surgical treatment of acute dissecting aneurysms, Arch. Surg 103 568 1971
38 McFarland J., Willerson J T., Dinsmore R E Austen W G Buckley M J Sanders C A., and DeSanctis R. W The medical treatment of dissecting aortic aneurysms, N Engl. J Med 286 115 1972
39 Dalen J E., Alpert J S Cohn L. H Black H and Collins J J Dissection of thoracic aorta—medical or surgical therapy? Am J Cardiol. 34 803 1974
40 Strong W W Moggio R A., and Stansel H C Jr Acute aortic dissection—twelve year medical and surgical experience J Thorac Cardiovasc Surg 68 815 1974
41 Bolooki H Management of aortic dissection J Fla Med Assoc 1979 (In press)
42 Rosenburg H L., and Mulder D G Dissecting thoracic aortic aneurysms, Arch Surg 105 19 1972
43 Parker F B Jr Neville J F Jr., Hanson E L., Mohiuddin S and Webb W R Management of acute aortic dissection Ann Thorac Surg 19 436 1975
44 Reul, G J., Jr Cooley D A Hallman G L., Reddy S B Kyger E R., III and Wukasch D C Dissecting aneurysm of the descending aorta Arch Surg 110 632 1975
45 Applebaum A., Karp R B., and Kirklin J W Ascending vs descending aortic dissections, Ann. Surg. 183 296 1976
46 Kidd, J N Reul G J., Jr., Cooley D A., Sandiford, F M., Kyger E R III and Wukasch D C Surgical treatment of aneurysms of the ascending aorta, Circulation 54(Suppl. III) 118 1976
47 Seybold Epting W., Meyer J Hallman G L., and Cooley D A Surgical treatment of acute dissecting aneurysms of the ascending aorta J Cardiovasc Surg (Torino) 18 43 1977
48 Mills, S E., Teja K. Crosby I K and Sturgill B C Aortic dissection surgical and nonsurgical treatments compared—an analysis of seventy four cases at the University of Virginia Am J Surg 137 240 1979
49 Thomas C S Jr Alford W C Jr Burrus G R Frist R A and Stoney W S The effectiveness of surgical treatment of acute aortic dissection Ann Thorac Surg 26 42 1978

Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978 Therefore all manuscripts must be accompanied by the following written statement signed by one author The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C V Mosby Company in the event the work is published The undersigned author warrants that the article is original is not under consideration by another journal and has not been previously published I sign for and accept responsibility for releasing this material on behalf of any and all co authors Authors will be consulted when possible regarding republication of their material

Clinical pharmacology of the new beta-adrenergic blocking drugs Part 11 Effects of oral labetalol in patients with both angina pectoris and hypertension a preliminary experience

Stanley Halprin, M D
William Frishman M D *
Marc Kirschner M D
Joel Strom M D
Bronx N Y

Beta adrenoceptor blocking drugs are widely accepted for the treatment of hypertension arrhythmias and angina pectoris[1,2] Labetalol 5 (1 hydroxy 2 [1 methyl 3 phenylpropyl) amino] ethyl salicylamide (Fig 1) is a recently developed drug which like propranolol blocks both beta 1 and beta 2 vascular and bronchial receptors[3,4] However labetalol is unique in that it also has both alpha adrenergic blocking properties and direct vasodilating activity[3,5] The beta blocking potency of labetalol is four to 16 times that of its alpha blocking potency

Alpha adrenergic blocking drugs have limited therapeutic application compared to beta adrenoceptor blocking drugs This may be in part because of the unwanted effects of reflex tachycardia and orthostatic hypotension which can aggravate coronary artery disease In selected patients with variant angina alpha blocking agents have been useful as adjunctive therapy Patients with coronary artery disease develop increased cardiovascular resistance following the cold pressor test[7] Phentolamine reverses this effect This latter finding raises the possibility that alpha adrenoceptor blockade may play a role in the prevention of myocardial ischemia[7,8]

Labetalol an alpha beta blocker has been shown to be a potent antihypertensive drug[4,9,10] Intravenous administration of labetalol in patients with angina pectoris resulted in a marked increase in exercise tolerance[11] In the present pilot study the effects of oral labetalol in patients who have both angina pectoris and essential hypertension were assessed

Methods

Patients Six male patients with stable angina pectoris and systemic hypertension were entered in the study The average age was 55 years (range 47 to 59 years) The diagnosis of angina pectoris was established by clinical history (symptoms and response to sublingual nitroglycerin) and by the development of typical angina pectoris with the treadmill exercise test In addition five of the six patients had an exercise induced ECG ST segment depression of at least 1 mm of the ischemic type The diagnosis of coronary artery disease was made by coronary angiography (a stenosis compromising the lumen of at least one major coronary artery by more than 75%) in three patients and by a previously documented myocardial infarction in the other three All patients

From the D[illegible] of [illegible] Medicine Albert Einstein College of Med[illegible]

Supported in part b[illegible] H[illegible]lth Servic[illegible] Tr[illegible] Grant HL 0[illegible] nd by [illegible] Pharmaceutical Company Bloomfield N J

Received for publication De[illegible]

Reprint request Wil[illegible]am Fr[illegible] Albert Ein[illegible] C[illegible]llege of Med[illegible] Bron N Y 10[illegible]

* Dr Frishman is a Tea[illegible]hing Sch[illegible] Am[illegible] n Heart Asso[illegible]tion

[illegible] The C V Mosby Co

had to have at least five attacks of angina pectoris a week for one month with no evidence for an accelerated course Hypertension was documented in all patients by an average 3 minute standing diastolic pressure of $\geq 90 \leq 110$ mm Hg (using Korotkoff Phase V) on at least two separate outpatient visits while untreated

Patients with the following conditions were excluded from the study coexistent valvular heart disease congestive heart failure bronchial asthma severe bradycardia (resting heart rate < 50 beats/minute) intermittent claudication and either myocardial infarction or coronary artery bypass within 3 months

None of the patients received medication during the trial other than the study drug and sublingual nitroglycerin Written informed consent was obtained in all instances

Experimental design This study was divided into three periods A three week placebo period in which patients received placebo* three times daily (t i d) was followed by a four week labetalol treatment period The dose of labetalol was titrated weekly (100 to 400 mg t i d) to achieve the optimal antihypertensive effect and improvement in the patient s anginal symptoms The optimal antihypertensive effect was defined as an average 3 minute standing diastolic blood pressure of < 90 mm Hg and at least a 10 mm Hg reduction from placebo baseline Improvement in angina was defined by a significant decrease in the number of anginal attacks and by a significant increase in exercise tolerance If the antihypertensive goal were achieved at a lower dose than the maximum but the angina did not improve the dose of labetalol was to be increased However this increase was only to be made if it was felt that the patient could tolerate it without developing clinical signs of hypotension At the end of this four week therapeutic period the dose of labetalol was tapered over a two day interval The patient was reassessed 1 to 4 days after cessation of labetalol and again in one week

Methods of observation All patients kept a detailed daily record of the angina attacks they experienced the number of nitroglycerin tablets taken and an estimation of the physical activity for that day Every week the patients were evaluated with a detailed history and physical examination which included measurements of

*Sch rng Corpo t n Bloomfi ld N J 0 003

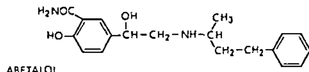


Fig 1 Chemical structure of labetalol

supine and standing (3 minute) heart rate and blood pressure Blood pressure and heart rate determinations were always made 2 hours after ingestion of placebo or labetalol which is the time of the peak pharmacological effect of labetalol [15] Patients also underwent multistage treadmill exercise studies (Bruce Protocol[16] each week) Complete blood counts urinalyses chest roentgenograms resting electrocardiograms and biochemical blood screening tests (total protein albumin calcium phosphate cholesterol triglycerides uric acid blood urea nitrogen glucose sodium potassium chloride total bilirubin alkaline phosphatase SGOT SGPT CPK LDH CO_2) were performed pre and post labetalol treatment

Exercise tests Multistage exercise testing following the Bruce protocol [8] was performed weekly with the use of a treadmill The blood pressure was measured every minute during exercise by the auscultatory method and the ECG was monitored on the oscilloscope The end point of exercise was angina pectoris defined by the patient s typical chest pain discomfort An abnormal electrocardiographic response was defined as a flat or downsloping ST segment depression of 1 mm of 0 08 seconds duration after the terminus of the QRS complex with the P Ta segment as the baseline of reference

Work performance was expressed in total minutes of treadmill exercise The product of heart rate and systolic blood pressure an indirect index of myocardial oxygen consumption [17] was calculated from measurements obtained at each one minute measuring interval

Statistical analysis Group means are presented with the standard error of the mean as the index of dispersion Comparison between treatment phases were made using Student s paired two tailed t test

Results

Effects on resting blood pressure and heart rate (Table I) There was a statistically significant reduction in the supine and standing systolic and

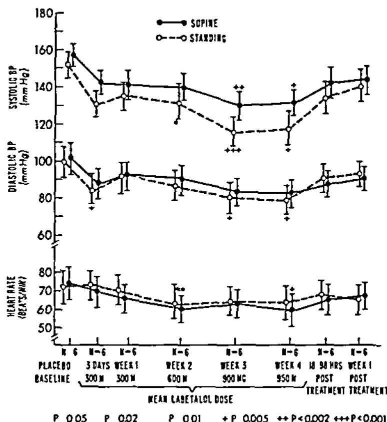


Fig 2 Effects of placebo and labetalol on resting supine and standing blood pressure and heart rate Compared to placebo a significant decrease in systolic and diastolic blood pressure is seen with initiation of labetalol therapy (300 mg /day) an effect which is augmented when higher doses of the drug are used A significant decrease in supine heart rate is seen with labetalol 600 to 900 mg /day compared to placebo There is no rebound in heart rate and blood pressure above placebo values one week post withdrawal

able I Effects of labetalol on resting heart rate and blood pressure in patients with both angina pectoris and hypertension

	Baseline (placebo) *N = 6*	*Peak dose labetalol (mean dose 950 mg)* *N = 6*	*Difference*	*Significance*
Supine				
Heart rate (beats/min)	768 ± 47	63.9 ± 3.5	−12.9 ± 2.5	p < 0005
Systolic BP (mm Hg)	158.8 ± 40	135.3 ± 9.9	−235 ± 4.5	p < 0005
Diastolic BP (mm Hg)	10364 ± 16	871 ± 2.1	−16.5 ± 36	p < 001
3 minute standing				
Heart rate (beats min)	75.9 ± 51	677 ± 31	−8.2 ± 4.3	NS
Systolic BP (mm Hg)	1546 ± 61	1216 ± 7.9	−330 ± 57	p < 0005
Diastolic BP (mm Hg)	1020 ± 17	831 ± 41	−189 ± 31	p < 0005

Mean ± standard erro f the m n

diastolic blood pressure from placebo baseline (Fig 2) After four weeks of labetalol treatment mean supine systolic blood pressure was reduced by 23.4 mm Hg and the standing systolic blood pressure fell by 33 mm Hg While there was a postural fall in systolic pressure this was not statistically significant Mean supine diastolic blood pressure was reduced by 16.5 mm Hg and standing diastolic blood pressure was reduced by 18.9 mm Hg Supine heart rate fell by 12.9 beats per minute which was statistically significant ($p < 0.005$) The standing heart rate was approximately 5 beats/minute higher than the supine heart rate The standing heart rate fell 8.3 beats

Table II Effects of labetalol on exercise tolerance and determinants of myocardial oxygen consumption

	Exercise time (min) N = 6	*Exercise peak systolic pressure mm Hg N = 6*	*Exercise peak heart rate beats/min N = 6*	*Exercise peak rate pressure product N = 6*
Baseline (placebo)	4.3 ± 0.9	188.3 ± 18.9	124.5 ± 9.9	23,708 ± 3,376
Peak dose labetalol (mean dose 950 mg)	6.3 ± 0.4	148.3 ± 17.8	118.0 ± 6.2	17,705 ± 2,560
Difference	*+2.0 ± 0.6*	*−38.3 ± 7.0*	*−6.5 ± 5.1*	*−6,003 ± 1,600*
Significance	p < 0.02	p < 0.005	NS	p < 0.02
	HR change from rest to Stage I beats/min N = 6	**HR change from rest to Stage II beats/min N = 4**	**Systolic BP change from rest to Stage I N = 6**	**Systolic BP change from rest to Stage II N = 4**
Baseline (placebo)	34.7 ± 6.6	42.0 ± 7.9	15.5 ± 7.9	38.7 ± 11.3
Peak dose labetalol (mean dose 950 mg)	29.5 ± 3.5	41.3 ± 4.7	5.0 ± 3.9	16.8 ± 9.9
Difference	−5.2 ± 5.3	−0.7 ± 3.9	−10.5 ± 6.3	−22.0 ± 5.6
Significance	NS	NS	NS	p < 0.05

Mean ± standard error of the mean

per minute but this was not a statistically significant fall

Effects on angina pectoris Subjective improvement was found in a significant reduction ($p < 0.05$) in the number of angina pectoris attacks (and nitroglycerin consumption) per week (8.5 ± 2.6 attacks at baseline and 1.0 ± 0.6 attacks after four weeks of labetalol treatment) The quality of life of the patients was enhanced they reported increased ability to perform activities of daily living All patients were Functional Class III (American Heart Association Critteria) on entry into the study and became Class II after four weeks of labetalol

Stress test results (Table II and Fig 3) The resting heart rate prior to the exercise stress test was decreased from placebo baseline by 10 ± 3.5 beats/minute which was statistically significant ($p < 0.02$) The heart rate was also significantly reduced at State I ($p < 0.02$) but not at Stage II of the Bruce protocol While there was an absolute reduction in heart rate there was no inhibition of the exercise induced increases in heart rate as measured by the beats/minute increase in heart rate from rest to Stage I and II at baseline and after four weeks of labetalol ingestion The peak heart rate achieved with exercise after labetalol therapy was not significantly different from placebo baseline even though total exercise time increased by 45%

The resting systolic blood pressure prior to the stress test was significantly reduced ($p < 0.001$) as was the systolic blood pressure at stage I and II ($p < 0.005$) However a significant inhibition of exercise induced increases in systolic blood pressure was found only at stage II ($p < 0.05$) no significant inhibition was found Stage I At Stage I the mean reduction in the rise from rest with placebo to the rise after labetalol was −10.5 mm Hg and the significant inhibition at Stage II was −22.0 mm Hg

With significant reductions in both heart rate and systolic blood pressure it is not surprising that the rate pressure product (heart rate × systolic blood pressure) is also significantly reduced at rest and during exercise following labetalol treatment ($p < 0.02$) It should be noted that even though the peak rate pressure product is significantly less ($p < 0.02$) than at placebo baseline the patients had a significant increase in their exercise tolerance

At the endpoint of the stress test there was no significant decrease in the magnitude of the ST segment depression However it should be remembered that exercise time significantly increased These findings are best illustrated in a patient with three vessel coronary artery involvement (Fig 4)

Effects of Labetalol Withdrawal (Table III Fig 3) One week following labetalol withdrawal there was a return of resting blood pressure heart rate and rate pressure product towards placebo

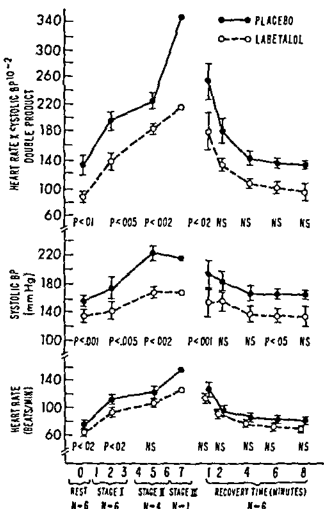


Fig 3 Effects of placebo and labetalol on systolic blood ure heart rate and rate pressure product during rest ercise and recovery Systolic blood pressure heart rate and te pressure product with exercise *(Stage I Bruce)* are significantly lower in labetalol treated patients when compared to placebo Following exercise the time for recovery to baseline heart rate and blood pressure is similar with placebo and labetalol.

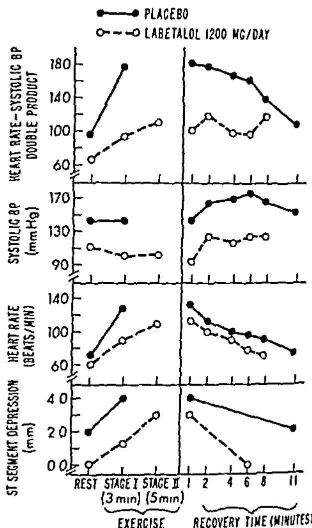


Fig 4 The effects of placebo and labetalol on systolic blood pressure heart rate rate pressure product and ECG ST segment depression during rest exercise and recovery in a representative patient (C M)

values without evidence of rebound Though not significant because of a high variability the mean values following withdrawal were lower that at placebo baseline

An increase in the frequency of anginal attacks and a reduction in exercise tolerance occurred following withdrawal when compared to the labetalol treatment pha e No patients developed unstable angina pectori or an acute myocardial infarction during the one week withdrawal interval

Adverse experiences Two patients complained of mild dizziness within one day of initiating labetalol treatment a reaction which was self limited and not seen later with higher doses One patient complained of mild fatigue at the highest labetalol dose which disappeared when the dose was reduced this same patient complained of decreased libido without ejaculatory dysfunction

Fundoscopic examinations did not detect any sign of oculotoxicity during the trial

There were no abnormalities found in the tests of liver and renal function There was no significant difference between triglyceride and cholesterol levels after labetalol treatment when compared with placebo

Discussion

Labetalol a unique beta adrenergic blocking agent with alpha adrenergic blocking properties is the forerunner of a new pharmacologic class of

Table III Effects of labetalol withdrawal (1 week post therapy) on blood pressure and heart rate compared to control

	Baseline (placebo) N = 6	*Labetalol uithdraual (1 ueek post therapy)*	*Difference*	*Significance*
Supine				
Heart rate (beats/min)	76.8 ± 4 7	71 4 ± 3 4	−5 4 ± 6 0	NS
Systolic BP (mm Hg)	158 8 ± 4 0	149 0 ± 4 6	−9.8 ± 5.9	NS
Diastolic BP (mm Hg.)	103 6 ± 1 6	95 8 ± 4 4	−7.8 ± 4 7	NS
3 mintue standing				
Heart rate (beats/min)	75 9 ± 5 1	72 5 ± 4 6	−3 4 ± 6 1	NS
Systolic BP (mm Hg.)	154 6 ± 6 1	144 9 ± 8.9	−9 7 ± 6 8	NS
Diastolic BP (mm Hg)	102 0 ± 1 7	97.2 ± 5 4	−4 8 ± 4 6	NS

Mean ± standard error of the mean

compounds Beta adrenergic blocking drugs have an established position in the treatment of essen tial hypertension and angina pectoris [1, 2] Recent evidence suggests that alpha adrenergic blockade may play a role in the prevention of myocardial ischemia by inhibiting neurogenic vasoconstric tion in coronary arteries [8, 18, 20] Reflex tachycardia and orthostatic hypotension have precluded their use as the sole agent in angina pectoris [2] Thus there is a potential advantage to the use of labetalol in the treatment of angina pecto ris

Labetalol in an antihypertensive agent of con siderable potency [9, 3] and appears to be more effective than propranolol in reducing blood pres sure [2, 23] Labetalol has been shown to be effica cious in hypertensive crises [24] pheochromocyto ma [25] and in many cases of drug resistant hyper tension [26]

Despite its widespread application in hyperten sive disease there has been little experience in patients with angina pectoris When administered intravenously to patients with angina pectoris it produced a significant increase in exercise toler ance but without any clearcut dose response relationship [4] Normotensive patients with coro nary artery disease receiving 200 mg of labetalol daily demonstrated increased exercise tolerance and electrocardiographic evidence of improve ment when compared with placebo [27]

The results of our preliminary study show that oral labetalol is an effective therapy for patients with both angina pectoris and hypertension The drug reduced resting systolic and diastolic blood pressure both supine and standing upon initia tion of therapy (100 mg t i.d) An augmentation of the antihypertensive effect was seen with higher doses (200 to 400 mg t i d) Unlike pure alpha adrenergic blocking agents [21] labetalol re duced the blood pressure without increasing the heart rate There was a slight reduction in stand ing heart rate and a significant reduction in supine heart rate The effects of the drug on systolic blood pressure were more pronounced in the standing position The differences between standing and supine systolic blood pressure deter minations following labetalol may relate to the vasodilatory effects of alpha adrenergic blockade which are more important in the standing posi tion Supine heart rate is significantly reduced while standing heart rate is not The differences between standing and supine heart rate determi nations following labetalol may relate to a com pensatory increase in rate with erect posture Postural hypotension was not seen with labetalol probably because the drug is a relatively weak alpha adrenergic blocker compared to phento lamine It follows then that the components of the reduction in rate pressure product with labe talol in the supine and standing positions differ in the upright position there is a greater reduc tion in systolic blood pressure and a lesser reduc tion in heart rate On the other hand in the supine position there is a lesser reduction in systolic blood pressure and a greater reduction in heart rate

There was a significant reduction in sponta neous attacks of angina pectoris and a significant increase in exercise tolerance with the peak labe talol dose

At a comparable level of exercise (Stage I—Bruce) the heart rate blood pressure and rate pressure product with labetalol were re duced compared to placebo The peak heart rate

blood pressure product achieved with exercise was lower following labetalol than with placebo despite a marked increase in exercise tolerance Thus in this small series labetalol appears to be an effective antianginal agent increasing exercise tolerance while reducing myocardial oxygen demands

There were no intolerable adverse reactions noted with the drug and one week following labetalol withdrawal there was no hyperadrenergic rebound state demonstrable Following withdrawal the heart rate and blood pressure were slightly lower (not significant) than baseline placebo levels (although significantly higher than with labetalol) This might reflect a prolonged action of the drug despite its short plasma half life,[15] or a training effect in the patients

Beyond the improvement in exercise tolerance and reduction in angina attacks there are other potential therapeutic advantages in the use of alpha beta adrenoceptor blocking agents in angina pectoris Since neurogenic vasoconstrictor impulses to the coronary resistance vessels are transmitted through sympathetic nerves acting upon alpha adrenergic receptors in the coronary vascular bed there may be an important role for alpha adrenergic blocking drugs in the prevention of coronary spasm and in the preservation of restricted coronary blood flow[4,5,16,28,31] This was suggested in a study by Mudge and associates where phentolamine was shown to block reflex coronary vasoconstriction regularly elicited by the cold pressor test Orlick and colleagues[6] also demonstrated that alpha adrenergic blockade was a useful adjunct in selected patients with variant angina

Beta adrenoceptor blocking drugs have been shown to decrease coronary blood flow in patients[30] Stimulation of beta$_2$ receptors which induced vasodilaton in coronary arteries can be blocked by propranolol Indeed blockade with nonselective beta adrenergic blockers may actually be detrimental in patients in whom ischemia is due to reduced oxygen delivery secondary to coronary spasm Non selective beta adrenoceptor blockade may allow the unopposed influence of coronary vasoconstrictor impulses to prevail Coronary blood flow was found to increase following intravenous labetalol administration in dogs[31] Labetalol with its alpha adrenergic properties may increase coronary blood flow while at the same time reduce myocardial oxygen demands in man

Labetalol may also have applicability in situations where other beta adrenergic blocking drugs are contraindicated Alpha adrenergic hypersensitivity has been shown to be important in many cases of bronchial asthma suggesting that the alpha adrenergic blocking activity of labetalol may be beneficial[34,3] In asthmatic patients with angina pectoris Skinner and associates[4] found that propranolol administered intravenously produced bronchoconstriction in asthmatic subjects Labetalol in equivalent cardiac beta adrenoceptor blocking doses did not cause bronchoconstriction Labetalol also lowers peripheral vascular resistance in contrast to other beta adrenergic blockers that elevate resistance[11] With its afterload reducing effects labetalol may be an ideal drug for patents with angina pectoris and hypertension associated with occult or mild congestive heart failure

Conclusions In this pilot study labetalol was found to be a safe and effective agent for reducing spontaneous attacks of angina pectoris improving exercise tolerance and reducing high blood pressure However, there are still many unanswered questions Double blind studies need to be initiated in patients with angina pectoris comparing labetalol to other beta adrenergic blocking agents nitrates and placebo The effects of labetalol on left ventricular function platelets and coronary blood flow in humans need to be elucidated The effects of labetalol in normotensive patients with angina pectoris also must be examined

Labetalol is an important pharmacological advance that provides an entirely new concept in management of patients with angina pectoris and hypertension—alpha beta adrenergic blockade

Summary

The safety and efficacy of oral labetalol an alpha beta adrenergic blocking drug was assessed in six patients with both angina pectoris and essential hypertension Patients received a placebo for 3 weeks which was followed by a 4 week titration of labetalol (100 to 400 mg three times a day) The dose was then withdrawn over a 2 day period With maximum doses of labetalol exercise tolerance as measured by multistage treadmill testing increased significantly com

pared to placebo ($p < 0.02$) At each exercise level (stage) the heart rate systolic blood pressure and rate pressure product were reduced with labetalol treatment There was no inhibition of exercise induced increases in heart rate However significant inhibition of the systolic pressure increment was seen at Stage II ($p < 0.05$) While peak heart rate was not significantly different from baseline the peak systolic blood pressure and rate pressure product were significanly reduced ($p < 0.02$) Labetalol treatment significantly reduced the number of weekly spontaneous angina attacks ($p < 0.05$) The resting supine and standing systolic and diastolic blood pressure were significantly reduced by labetalol ($p < 0.01$) There was no significant reduction in the standing heart rate but the supine heart rate was significantly reduced ($p < 0.005$) There were no rebound hyperadrenergic effects following labetalol withdrawal When used alone in patients with both angina pectoris and systemic hypertension oral labetalol is a safe and effective drug for reducing the symptoms of angina pectoris improving exercise tolerance and lowering high blood pressure

REFERENCES

1 Frishman W., and Silverman R Clinical pharmacology of the new beta adrenergic blocking drugs. Part 2 Physiologic and metabolic effects AM HEART J 97 797 1979

2 Frishman, W., and Silverman, R Clinical pharmacology of the new beta adrenergic blocking drugs Part 3 Comparative clinical experience and new therapeutic applications AM HEART J 98 119 1979

3 Brittain R T and Levy G P A review of the animal pharmacology of labetalol a combined α and β adrenoceptor blocking dru~ Br J Clin Pharmacol. 3(Suppl. 3) 681 1976

4 Frishman W., and Halprin S Clinical pharmacology of the new beta adrenergic blocking drugs Part 7 New horizons in beta adrenoceptor blockade therapy Labetalol, AM HEART J 98 660 1979

5 Johnson G L. Prioli N A. and Ehrreich S J Antihypertensive effects of labetalol (Abstract) Fed Proc 36 1049 1977

6 Orlick A. E., Ricci, D R Cipriano P Guthaner D and Harrison D C The role of alpha adrenergic receptors in the pathogenesis of coronary artery spasm Clin Res 25 456 1977

7 Mudge G H Jr Grossman, W Mills, R M J Lesch, M and Brauwald, E Reflex increase in coronary vascular resistance in patients with ischemic heart disease N Engl. J Med. 295 1333 1976

8 Hillis L. D., and Braunwald E Coronary artery spasm, N Engl J Med 299 695 1978

9 Mehta J., and Cohn J N Hemodynamic effects of labetalol an alpha and beta adrenergic blocking agent in hypertensive subjects Circulation 55 370 1977

10 Koch, G Haemodynamic effects of combined α and β adrenoceptor blockade after intravenous labetalol in hypertensive patients at rest and during exercise Br J Clin. Pharmacol. 3(Suppl. 3) 725 1976

11 Prichard B N C., and Boakes, A J Labetalol in long term treatment of hypertension Br J Clin. Pharmacol. 3(Suppl. 3) 743 1976

12 Bolli, P., Waal Manning H J., Wood A J., and Simpson F O Experience with labetalol in hypertension Br J Clin. Pharmacol. 3(Suppl 3) 765 1976

13 Joekes, A.M., and Thompson F D Acute haemodynamic effects of labetalol and its subsequent use as an oral hypotensive agent Br J Clin Pharmacol 3(Suppl. 3) 789 1976

14 Boakes, A. J., and Prichard B N C The effect of AH 5158 pindolol, propranolol, d propranolol on acute exercise tolerance in angina pectocis Br J Pharmacol 47 673 1973

15 Martin, L. E., Hopkins, R., and Bland, R.. Metabolism of labetalol by animals and man Br J Clin. Pharmacol. 3(Suppl. 3) 695 1976

16 Bruce R A. Progress in exercise cardiology *in* Progress in Cardiology Vol. 3 Yu P N., and Goodwin J F., eds., Philadelphia, 1974 Lea & Febiger pp 113

17 Robinson B F The mode of action of beta antagonists in angina pectoris, Circulation 35 1073 1967

18 Schwartz P J and Stone H L Tonic influence of the sympathetic nervous system on myocardial reactive hyperemia and on coronary blood flow distribution in dogs, Cir Res. 41 51 1977

19 Mohrman D E and Feigl E O Competition between sympathetic vasoconstriction and metabolic vasodilation in the canine coronary circulation Circ. Res. 42 79 1978

20 Murray P A., and Vatner S F Alpha receptor attenuation of coronary vascular response to severe spontaneous exercise Fed. Proc 37 235 19 8

21 Berlin L. J and Juel-Jensen B E α and β adrenoceptor blockade in hypertension Lancet 1 979 1972

22 Pugsley D J., Armstrong B K., Nassim M A., and Beilin, L. J Controlled comparison of labetalol and propranolol in the management of severe hypertension Br J Clin Pharmacol. 3(Suppl. 3) 777 1976

23 Trust P M., Rosei, E. A., Brown J J., Fraser R., Lever A. F., Morton, J J., and Robertson J I S Effect of blood pressure angiotensin II and aldosterone concentrations during treatment of severe hypertension with intravenous labetalol comparison with propranolol, Br J Clin Pharmacol. 3(Suppl. 3) 799 1976

24 Ronne-Rasmussen J O., Andersen, G S., Bowal Jensen N and Andersson E Acute effect of intravenous labetalol in the treatment of systemic arterial hypertension Br J Clin Pharmacol 3(Suppl 3) 805 1976

25 Rosei, E A Brown J J., Lever A F., Robertson A S., Robertson, J I S., and Trust P M.. Treatment of phaeochromocytoma and of clonidine withdrawal hypertension with labetalol, Br J Clin Pharmacol 3(Suppl. 3) 809 1976

26 Dargie H J Dollery C T., and Daniel J Labetalol in resistant hypertension Br J Clin. Pharmacol. 3(Suppl. 3) 751 1976

27 Brevetti, G., Chiariello M., Renyo F., Chiariello L. Paudice G., Laracetta, G., and Condorelli, M Labetalol in coronary artery disease Abstracts of the VIII World Congress of Cardiology 1 194 1978

28 Pitt, B., Elliot, E C., and Gregg, D E. Adrenergic receptor activity in the coronary arteries of the unanesthetized dog Circ Res. 21 75 1967

29 Levene D L and Freeman M R Alpha adrenoceptor mediated coronary artery spasm J A M A 236 1018 1976
30 Rubio R., and Berne R Regulation of coronary blood flow Progr Cardiovasc Dis 28 105 1975
31 Klocke F J Mates R E Copley D P and Orlick, A E Physiology of the coronary circulation in health and coronary artery disea e in Progress in Cardiology Vol 5 Yu P., and Goodwin J F eds Philadelphia 19 6 Lea & Febiger pp 1
32 Braunwald E Coronary artery spasm and acute myocardial infarction–new possibility for treatment and prevention N Engl J Med 299 1101 1978
33 Maxwell G M Effects of alpha and beta adrenoceptor antagonist (AH 5158) upon general and coronary hemodynamics of intact dogs, Br J Pharmacol 44 370 1973
34 Richardson P S and Sterling G M Effects of β adrenergic receptor blockade on airway conductance and lung volume in normal and asthmatic subjects Br Med J 3 143 1969
35 Fleisch J H Maling H M and Brodie B B Evidence for existence of alpha adrenergic receptors in mammalian trachea Am J Physiol 218 596 19 0
36 Bewtra A Longo F Adolphson R and Townley R Quantitative determination of alpha adrenergic receptor activity in human trachea *in vitro* J Allergy Clin Immunol 55 93 1975
37 Patel K R and Kerr J W Alpha receptor blocking drugs in bronchial asthma Lancet 1 348 19 5
38 Geumei A Miller J R and Miller W F Effects of phentolamine inhalation on patients with bronchial asthma Br J Clin Pharmacol 2 539 1975
39 Henderson W R Shelhamer J H Reingold D B Smith, L J Evans R and Kaliner M Alpha adrenergic hyperresponsiveness in asthma N Engl J Med 300 642 1979
40 Skinner C Gaddie J and Palmer K N V Comparison of intravenous AH 5158 (ibidomide) and propranolol in asthma Br Med J 2 59 1975
41 Sweet C S Solar J and Gaul S L Peripheral vasodilator and β adrenoceptor blocking properties of several β adrenoceptor antagonists Clin Exp Hypertension 1 449 1979

Annotations

Coronaviruses in Balkan nephritis

Viruses found in the kidneys were for a long time considered trivial symbionts, a viral flora. Only recently has it been recognized that these viruses might be subtle pathogens, possibly involved in slow initiation of progressive renal failure. Electron microscopic studies have revealed the presence of virus like particles in the kidneys of Balkan nephritis (BN) patients,[1] suggesting the implication of coronaviruses in renal pathology. However, the presence of viruses in tissues does not alone establish causation. The involved virus could not be isolated as yet, but even the successful recovery of an agent from the kidneys would provide a very low order of evidence for the purpose of proving causality. In an earlier paper we described our program of work on the possible viral etiology of BN and presented negative results on attempts at virus isolation and identification of antibody reactivity to selected viral antigens. Because of the suggestion that BN in man might be caused by a slow porcine coronavirus infection, this second progress report of our results is in order.

In the absence of virus isolations, emphasis has been placed on seroepidemiological investigations. Antibodies have been measured by complement binding, hemagglutination inhibition, and by single radial hemolysis in gel in serum specimens of 34 BN patients, their relatives sharing their housing and living conditions, and of 67 controls matched for age and sex. Sera from 21 pigs kept by patients were also examined. All sera were heat inactivated before testing. Antigens used in this survey were prepared in our laboratory with human, avian, and porcine strains of coronavirus. The prevalence of antibodies to pig coronavirus was tested with the hemagglutinating encephalomyelitis virus 2063/68 strain. This strain was originally isolated from piglets with vomiting and wasting disease and it is closely related to, if not identical with, the hemagglutinating encephalomyelitis virus of swine and also related antigenically to the transmissible gastroenteritis virus of pigs.

None of the pigs from which serum was taken had either vomiting and wasting disease, transmissible gastroenteritis, infantile pyloric stenosis, or encephalitis. Antibodies to the 2063/68 virus strain were found in serum from only one animal, at a titer of 40. Human sera, whether of BN patients or of controls, yielded constantly negative results with this virus. Further investigations with the use of the OC 43 and the 229 E strain of human coronavirus, and of the Beaudette and the Massachusetts 41 strain of avian infectious bronchitis virus revealed so far no statistically significant differences of the incidence of antibodies, the geometrical mean titer, or the frequency of elevated titers between BN and control sera.

These findings must be interpreted with caution because of the antigenic diversity of coronaviruses, of the lack of antigens for strains having fastidious growth requirements, and because of the necessity to perform different assay procedures according to the various antigens used. The complement fixation reaction seems rather unsuitable for serosurveys, since complement fixing antibodies are relatively short lived. Neutralization is effective but expensive, slow, and tedious, while the hemagglutination inhibition test is impracticable with non hemagglutinating coronavirus strains. Moreover, in a chronic viral infection there is always the possibility that antibody production may be masked by complete absorption of circulating antibody by excess antigen. It has to be remembered that the immunofluorescence test actually disclosed in the kidneys of BN patients a granular fluorescence along the basement membrane of the glomeruli, but the nature of the deposited immune complexes has not been investigated.

Coronaviruses are emerging as important causes of common cold like illness and are assumed to be involved in non bacterial gastroenteritis in humans. Lately, their possible role in chronic renal disease has also been suggested. Understanding of the behavior and role of these viruses has been hampered greatly by the difficulties in propagation encountered in the laboratory. If the agent involved in the etiology of BN is an animal RNA virus, then it would account for the predominant rural distribution of the disease. Our results indicate that the examined BN patients have had no contact with porcine coronaviruses and they have experienced infections with human and avian coronavirus strains in the same manner and at a rate similar to that found in the control group. It appears, therefore, that the virus-like particles found in renal tubular epithelial cells of BN patients are of an antigenically unrelated strain or a different type. The suspected natural focality of BN (involving for instance some rodent coronavirus) would explain the restricted geographical distribution of this disease and its dependence on ecological factors. Since the mouse brain grown strain OC 43 consistently fixes complement at low levels with antisera hyperimmune to various strains of mouse hepatitis virus, it seems unlikely that this virus would be involved either. Further search for corona and other RNA viruses of rodents in the endemic area, screening of human sera for antibodies to such strains, and studies to identify their role in BN seem indicated. At the present time the role of coronaviruses in BN remains uncertain.

Leonida Georgescu, M.D., Ph.D.
Department of Pathology
Timişoara Medical Institute, Timişoara
Peter Diosi, M.D., Ph.D.
Ioan Buţiu, M.D., Ph.D.
Litia Plavoşin, M.D., Ph.D.
Georgeta Herzog, D. Chem.
Virology Unit, Department of Epidemiology
The Medical Research Center
Timişoara, Romania

Strains of coronavirus were kindly provided by Dr. D. J. Alexander, Central Veterinary Laboratory, Weybridge, England; by Dr. R. S. Hopkins, Southeast Poultry Research Laboratory, Athens, Ga., U.S.A.; by Dr. H. S. Kaye, Center For Disease Control, Atlanta, Ga., U.S.A.; by Dr. K. J. Sørensen, State Veterinary Institute for Virus Research, Lindholm, Denmark; and by Dr. D. A. J. Tyrrell, Clinical Research Centre, Harrow, England.

0002-8703/80/030397 + 0[illegible] $00.[illegible]0/0 © 1980 The C. V. Mosby Co.

REFERENCES

1. Apostolov K., Spasic P and Bojanic N Evidence for viral aetiology in Endemic (Balkan) nephropathy Lancet 2 127 1975
2. Austwick P K C Balkan nephropathy Proc R Soc Med 68 219 1975
3. Diosi P Plavoşin L and Arcan P Propagation of mouse cytomegalovirus in murine kidney epithelium Rev Roum Virol 25 91 1974
4. Georgescu L and Diosi P Balkan nephritis a synthetic view of 50 studied cases Morphol Embryol (Buch) 22 13 1976
5. Georgescu L Diosi P Buţiu I Plavoşin L and Herzog G Porcine coronavirus antibodies in Endemic (Balkan) nephropathy Lancet 1 163 1978
6. Georgescu L Diosi P Buţiu I Plavoşin L and Herzog G Viruses and causation of Balkan nephropathy Ciba Foundation Symposium on Balkan nephropathy London June 1978
7. Georgescu L Litvac B Diosi P Plavoşin L and Herzog G Viruses in Endemic (Balkan) nephropathy Lancet 1 1086 1976
8. Georgescu L Litvac B Diosi P Plavoşin L and Herzog G Viruses in Balkan nephritis AM HEART J 94 805 1977
9. Georgescu L Litvac B Manescu N Petrovici A Schwartzkopf A and Zosin C Particules virales dans la rein de la néphropathie endémique Sem Hop Paris 46 3526 1970
10. Riski H Hovi T Vaananen P and Penttinen K Antibodies to human coronavirus OC 43 measured by radial haemolysis in gel Scand J Infect Dis (In press)
11. Schild G C Pereira M S and Chakraverty P Single radial haemolysis a new method for the assay of antibody to influenza haemagglutinin Applications for diagnosis and seroepidemiologic surveillance of influenza Bull WHO 52 43 1975
12. Tomescu E Constatarea de particule de tip viral intr un caz de nefropatie endemica familiala Morfol Norm Patol (Buch) 15 365 1970

Cigarette smoking and coronary heart disease new evidence and old reactions

Although there is little doubt that cigarette smoking is a causal factor in lung cancer and chronic obstructive lung disease there has been less agreement about the causal nature of the often found relation between cigarette smoking and coronary heart disease (CHD) for the following reasons The relation between smoking and CHD has not generally been strong—usually smokers have shown about a twofold excess incidence over non smokers, in contrast with the tenfold increase for lung cancer Relatively weak associations are often attributable to some underlying characteristic Thus it has been proposed that some constitutional or genetic factors are present in the smoker that both lead him or her to smoke and predispose to CHD This counterhypothesis has had some distinguished support going back at least to the noted statistician R A Fisher who was primarily concerned with smoking and cancer Another problem with the evidence concerning smoking and CHD [illegible] that the relationship is not found in all study populations For example in the seven country collaborative [illegible] Keys and associates U S railroad workers sh[illegible] CHD relationship but using similar data coll[illegible] in Finland the Netherlands, Italy [illegible] and Japan did not and these countries rang[illegible] high CHD incidence Another troublesome finding [illegible] smoking tends to be a weaker predictor [illegible] persons than in young and middle aged adult [illegible] of the risk factor [illegible] does not seem [illegible] with the generally held notion that smoking acts [illegible] CHD largely by precipitating acute events su[illegible] myocardial infarction and sudden cardiac death Old[illegible] with advanced atherosclerosis should be especially [illegible] the effect

Then again the mechanism by which smoking promotes CHD has not been well established although vascular damage from carbon monoxide deleterious effects of increased catechol amine release and promotion of thrombotic tendencies have been proposed Finally data from studies of smoking-discordant identical twins where the smokers and nonsmokers are genetically the same have not shown the degree of association between smoking and CHD as has been found in the general population where there is obviously no such genetic matching Nevertheless because of small numbers of subjects, the twin data to date are too meager to be conclusive in this regard and a number of methodologic questions have been raised about these studies Similar considerations apply to the association of smoking with total mortality of which deaths from CHD (but not from lung cancer or bronchitis) constitute a major component

Probably the only study design that would convince virtually everyone that cigarette smoking itself does contribute to CHD would be a large scale controlled experiment in which young healthy persons were randomly assigned to smoke or not and in which they obeyed their assignment and were followed up over most of their lifetimes for CHD development Such a study would be unethical and impossible to carry out Therefore we must do the best we can with observational rather than experimental studies

We recently published an observational study of the relationship of cigarette smoking to total and CHD mortality that took advantage of a large body of data that was collected on 4004 middle aged cigarette smokers ex smokers and non smokers who responded to periodic urgings to take multiphasic health checkups Because of the recruitment effect

0002-8703/80/030398 + 0_$00.20/0 © 1980 The C V Mosby Co

the degree of non response 17 per cent was relatively small for this type of study More important the checkups provided a rich source of computer stored data that could be used to test a variety of reasonable alternatives to cigarette smoking itself as the explanation for the higher death rates in smokers observed during an 11 year follow up period Thus we considered not only age sex race and other established CHD risk factors but also educational level alcohol use marital status presence of serious disease exposure to a variety of occupational hazards and medicinal drugs, and questionnaire responses suggesting depression and other emotional problems Neither individually nor in combination did the 48 characteristics considered explain the association After adjustment for these variables the smokers total death rate was still 2 1 times higher than that of non smokers and the adjusted smoker/non smoker ratio for CHD death was 3 6

I hope that this type of study can be repeated by others with extensive baseline information and follow up data available on smokers and non smokers If more evidence against alternative explanations is accumulated the case for the responsibility of smoking itself will be further strengthened On the other hand it is still possible (though unlikely in my opinion) for the counterhypothesis to be confirmed Or perhaps smoking fosters the development of CHD in some persons and not in others Additional data about pathogenesis should help explain the inconsistencies in the smoking-CHD evidence

It would be best if such studies can be carried out in a spirit of scientific inquiry rather than in an attempt to prove that cigarettes do or do not cause CHD Considerable suspicion is raised and emotional reactions are generated when one tries to perform objective research about controversial habits such as smoking or alcohol use In the extensive publicity of our study by the media much was made of the fact that the financial support came from the tobacco industry (Actually the grant was from the Council for Tobacco Research U S.A which is supported by tobacco companies but whose decisions as to what research to support are made by a group of distinguished physicians and scientists serving on its scientific advisory board There were no requirements or "strings attached to the grant and we felt no pressure from this granting agency to report or publish only findings favorable to smoking) Thus our report which would be interpreted as unfavorable to cigarette smoking was considered credible because of its ultimate financial support by the tobacco industry If the study had turned out differently and revealed some characteristics that explained away the smoking-mortality relationship many would not have believed the result and we would have been accused of being bought and paid for by the tobacco industry Such an accusation was made by a reviewer for a different journal when we submitted a paper that raised questions about the comparability of persistent smokers and ex smokers with respect to CHD risk status determined at a time when all were still smoking

We have had similar experiences in studying the relation of alcohol to cardiovascular disease About one year ago a well known syndicated newspaper columnist raised questions about our credibility in this area since our study was funded in part by a grant from the U S Brewers Association another organization whose research funding decisions are made by distinguished physicians and scientists with no attempt to influence the reports of grantees. The columnist had failed to note that our observation of a negative relation between alcohol consumption and risk of myocardial infarction suggesting the possibility of a protective effect was made under a research contract funded by the U S Government (That we should suggest such a possibility also led to angry letters and comments at meetings by persons who obviously did not want to hear anything favorable about alcohol) Ironically our observation that alcohol use is correlated with elevated blood pressure a possible detrimental effect, was from the study supported by the U S Brewers Association.

There are no easy solutions to the suspicion of bias raised by the source of financial support It has been suggested that a researcher should accept no funding from an interested industry Yet this is an important and valuable source of support in these times of tight money Interposing an advisory committee between industry and an investigator may help but some critics will assume that the advisory committee has also been bribed It must also be recognized that many skeptics believe that the government voluntary health agencies and various foundations have their own axes to grind and favor research that supports their interests and programs So suspicion can thus be raised about studies supported by any source Ultimately we must all rely on the integrity and objectivity of the researcher and the basic scientific process of repetition of studies by other investigators

Gary D Friedman M.D
Dept of Medical Methods Research
Kaiser Permanente Medical Care Program
Oakland Calif 94611

REFERENCES

1 Fisher R. A Smoking the cancer controversy Some attempts to assess the evidence London 1959 Oliver and Boyd
2 Keys A Coronary heart disease in seven countries Circulation 41(Suppl I) I 184 1970
3 Kannel W B Castelli W P., and McNamara P M Cigarette smoking and risk of coronary heart disease epidemiologic clues to pathogenesis the Framingham study National Cancer Institute Monograph 28 June 1968 pp 9 20
4 Cederlof R Friberg L. and Lundman T The interactions of smoking environment and heredity and their implications for disease etiology a report of epidemiological studies on the Swedish twin registries Acta Med. Scand Suppl 612, 1977
5 Hrubec Z Cederlof R and Friberg L. Background of angina pectoris social and environmental factors in relation to smoking Am J Epidemiol 103 16 19 6
6 Ramstrom L. M The Swedish twin study—publicity and criticism World Smoking and Health 3 14 1978
7 Friedman G D A potential pitfall in studying trait discordant twins Am J Epidemiol. 105 291 1977
8 Friedman G D Dales, L G and Ury H K Mortality in middle aged smokers and nonsmokers N Engl J Med 300 213 1979
9 Klatsky A L., Friedman G D and Siegelaub A. B Alcohol consumption before myocardial infarction results from the Kaiser Permanente epidemiologic study of myocardial infarction Ann Intern Med 81 294 1974
10 Klatsky A. L. Friedman G D Siegelaub A. B and Gerard, M J Alcohol consumption and blood pressure Kaiser Permanente multiphasic health examination data N Engl. J Med 296 1194 1977

Coronary care—the limits?

Anyone who has practiced medicine in a hospital environment in the last 20 years will recall the helplessness of the cardiac arrest situation and contrast this with the efficient handling of that same occurrence in Coronary Care Units This improvement developed logically from the recognition that the common cause of death after myocardial infarction ventricular fibrillation can be reversed electrically and that these patients subsequently do relatively well These units appeared to halve hospital mortality rates and in the United Kingdom many District General Hospitals have such units usually supervised by a team of general physicians, many of whom have interests outside cardiology Are these developments justified in the light of more recent data?

Few would dispute that general physicians run efficient units or that if they are necessary these units should be situated in the District General Hospital setting This is where most hospital medicine is practiced and where most patients who have sustained a myocardial infarction will receive care Recent figures indicate no significant difference between ward and Coronary Care Unit mortality rates, and this together with the suggestion that some antidysrhythmic drugs are *effective prophylactically* suggests that the concept of the Coronary Care Unit requires reappraisal. These observations are invalid however because wards have benefited by the dissemination of equipment and expertise from Coronary Care Units. This is important as a feature of C C U s is the manner in which they have crystallized the approach to the coronary patient and disciplined those responsible for it—medical and ursing staff The contribution of the latter has been particu rly valuable and is another example of the way in which the underrated potential of the nurse has been channelled to advantage It would indeed be surprising if the impact of a C C U was not felt throughout a hospital and if ward mortality rates have fallen it is an argument for maintaining the C C U and not for removing it Moreover there is no good evidence that antidysrhythmic therapy is of prophylactic value There is certainly a need to design and staff C C U s less expensively remembering that their cost must be considered against that of the alternative—monitoring and nursing patients scattered throughout a department

The problem with C C U s is that their impact on mortality rate after M I is limited by the fact that 40 to 75% of deaths occur within the first hour Patients are rarely admitted as quickly as this. Indeed 60% of deaths occur outside the hospital hence the efforts to extend resuscitative facilities with mobile units (M C C U s) There is no doubt that with enthusiasm drive and resources these units can have a small but significant impact on mortality Where resources are extensive and include efforts to alter public attitudes the results can be very rewarding as has been found in Seattle In ordinary hands, however M C C U s have often been disappointing and workers in Nottingham suggest that hospital based domiciliary services called by family doctors to cases of suspected myocardial infarction are unlikely to make a contribution to the lowering of mortality Once more this is due to delay in reaching the patient. Not surprisingl at an especially difficult time for competing priorities, there is indecision about implementing M C C U s no encouragement b those responsible for health services and consequently no resources. Certainly there is no prospect of launching into the type of activity established in Seattle in the United Kingdom

Another approach to the management of these patients is based on the long tradition of family medicine in the United Kingdom There are now three studies which indicate that certain patients with M I can be kept at home Though there are weaknesses to all three studies together they suggest that home management is safe for patients who have already survived about four hours before coming under medical care Such management is nonetheless inappropriate for those with cardiac complications such as dysrhythmias, associated medical disorders or unsuitable social circumstances The Nottingham group excluded from their trial 74% of the cases they visited at home on these grounds. In addition 20 to 40% of patients are not at home when they are stricken Clearly quite a sizeable proportion of patients with M I will always require hospital admission but it is likely that many patients are admitted to the hospital unnecessarily There are also some family doctors who feel they should play a very important role where patients are seen within the first hour or two. *Colling advocates that the family doctor who is usually called* first, should attend immediately at the slightest suspicion of a myocardial infarction and stay with his patient over the two hours or so from the onset of the attack During this period he would reassure provide efficient analgesia monitor and treat dysrhythmias medically An important aspect of early management is as little movement of the patient as possible It remains to be shown whether it is more important to keep these patients still or get them to a defibrillator quickly Deaths occurred during ambulance transfer in the Teesside survey but the experience of mobile units suggests that this is not a problem in patients adequately managed prior to transportation

There are certain problems with this approach however It is unlikely that the majority of family doctors are confident enough to cope in the manner advocated by Colling and the use of antidysrhythmic drugs in general practice is potentially hazardous It is estimated that a family doctor with an average list will come across perhaps a handful of cardiac arrest situations per year with of course variable success, perhaps too small to motivate him It would certainly provide insufficient experience Though the speed with which a family doctor responds to a call can be improved, it must be emphasized that the main cause of delay is patient delay which is difficult though not impossible to change Of more importance the family doctor service has had to organize itself in an atmosphere of increasing health demands and expectations in a way (including the use of an out-of hours deputizing service) which leaves little room for a rapid response to all potential coronary incidents and even less for the continuing time-consuming management in the home which is advocated. Additional time would also have to be found for the necessary training program Nonetheless the message of intensive involvement by the family doctor as early as possible in the management of patients with M I should be encouraged but must include a defibrillator as the prime piece of resuscitative equipment Access to this should not be a

0002-8703/80/030400 + 02$00.20/0 © 1980 The C V Mosby Co

problem since there is no reason why groups of family doctors should not organize their routine around this equipment as some have already done This does require that family doctors think outside the limits of their own practices Whether a doctor should extend his initial primary resuscitative role with continuing home management is an open question Most doctors will not have the time for this and additionally it seems illogical to deprive a patient of a defibrillator after about two hours from the onset of the attack Transfer to a C C U preferably using the services of an M C C U would seem more prudent This faster tempo in the management of the infarct situation would make the case for the latter stronger

In summary recent community studies suggest that a group of patients can probably be kept safely at home after a myocardial infarction These results have been interpreted by some as a prescription for leaving all such patients at home There is no evidence to support this and such an approach tends to remove the aura of urgency from what is a very urgent situation The main objective must still be to get a defibrillator to the patient within two hours of the incident Though there will always be exceptions which must be encouraged it would seem that in general the C C U and M C C U have reached the limit of what they can achieve towards this goal It seems important therefore to encourage the call by certain family doctors for a leading role in primary resuscitation after myocardial infarction and this clearly is an area with a potential to affect mortality rates which has not been fully explored The difficulties of this particular approach are not insuperable but only time will tell if family doctors are able to respond and if their response is worth while

A W Dellipiani MD FRCP
Department of Medicine
North Tees General Hospital
Hardwick Stockton-on Tees
Cleveland TS19 8PE
N Yorkshire
England

REFERENCES

1 Hofvendahl S Influence of treatment in a coronary care unit on prognosis in acute myocardial infarction—a controlled study in 271 cases Acta Med Scand Suppl. 519 9 1971
2 Colling W A., Dellipiani, A W Donaldson R J and McCormack P Teesside Coronary Survey An epidemiological study of acute attacks of myocardial infarction, Br Med J 2 1169 1976
3 Hill J D., Holdstock G and Hampton J R Comparison of mortality of patients with heart attacks admitted to a Coronary Care Unit and an ordinary ward Br Med J 2 81 1977
4 Zainal, N., Griffiths, J W., Carmichael J D S Besterman F M M Kidner P H Gillham A. D and Summers, G D Oral disopyramide for the prevention of arrhythmias in patients with acute myocardial infarction admitted to open wards Lancet 2 887 1977
5 Coronary Care in the Community Colling W A., ed. London 1977 Croom Helm
6 Pantridge J F., and Geddes, J S A mobile intensive care unit in the management of myocardial infarction Lancet 2 217 1967
7 Mackintosh A F and Crabb M E Grainger R. Williams, J M., and Chamberlain D A. The Brighton resuscitation ambulances Review of 40 consecutive survivors of out-of hospital cardiac arrest, Br Med J 1 1115 1978
8 Cobb L A Baum R S Alvarez H and Schaffer W A Resuscitation from out-of hospital ventricular fibrillation 4 years follow up Circulation 51 and 52 Suppl III 223 1975
9 Hampton J R and Nicholas C Randomised trial of a mobile coronary care unit for emergency calls, Br Med. J 1 1118 1978
10 Mather H G Morgan D C Pearson M G Read K L. Q Shaw D B Steed G R Thorne M G Lawrence C J and Riley I S Myocardial infraction A comparison between home and hospital care for patients Br Med J 1 925 1976
11 Dellipiani, A W., Colling W A., Donaldson, R J., and McCormack P Teesside Cornary Survey—fatality and comparative severity of patients treated at home in the hospital ward and in the Coronary Care Unit after myocardial infarction Br Heart J 39 1172 1977
12 Hill J D Hampton J R and Mitchell J R A A randomised trial of home versus-hospital management for patients with suspected myocardial infarction Lancet 1 837 1978
13 Adgey A. A J Allen J D., Geddes, J S., James R G G Webb S W Zaidi S A and Pantridge F F Acute phase of myocardial infarction Lancet 2 501 1971

Of bibliographies

In recent years the references listed in the bibliographies of reports in medicine make readers wonder what is the purpose of a bibliography It would seem that the purpose of a bibliography should be to orient, in proper perspective and time the study being reported with related studies previously reported by others Certainly a bibliography is not to be employed as a vehicle to indicate or suggest that the study being reported is partly or entirely new when it isn t Nor is it proper to select references so as to imply that other authors originally described or discovered a phenomenon in medicine or science when they didn t Nepotism certainly is not to be accepted or *condoned in science* Editors and reviewers are unable to evaluate bibliographies of all reports satisfactorily The quality and accuracy of a bibliography reflects the quality and accuracy of the data of the study and the interpretation of the data When the bibliography is inaccurate then how reliable are the data of the study and the reported *interpretations*? Readers are regularly impressed

0007-8703/80/030401 + 0?500 0/0 © 1980 The C. V. Mosby Co

with the failure of current reports to consider reports of the same type of study with similar results from the remote past It would appear that authors tend to depend entirely on the references available through such services as Medline which catalogues publications of only the past 5 years or so A thorough complete and careful review of the medical literature on any subject is an ordeal which is difficult and time-consuming but which is extremely informative educational and proper After all reports regardless of when they were published are there for critical scientists and physicians to observe and evaluate Surely a thorough review of the literature would frequently reveal that a study similar to the one being reported had been reported many years earlier This would improve the quality and reliability of reports and certainly would orient them in their proper temporal perspective Few studies and findings are entirely new A careful review of the entire literature will reveal the importance of a study and whether or not it presents anything new as well as the need if any for its publication Nepotism in publication is an error which reflects extremely unfavorably on the authors. The bibliography and the use of references reflect the quality and accuracy of the data and surely the character of the author or authors and the total value and importance of a report An inaccurate or inadequate bibliography certainly reflects an inaccurate and inadequate report The bibliography is a part of the report What is important is how the bibliography is used by the author

George E Burch MD
Tulane University School of Medicine
and Charity Hospital of Louisiana
New Orleans La

Letters to the Editor

Bradyarrhythmia after digitalis—chronic cardiotoxicity?

To the Editor

I enjoyed your Annotation on digoxin-diuretic cardiomyopathy and I completely agree with your statement that "it is not possible to digitalize a patient properly with the use of digoxin

Concerning the digoxin cardiomyopathy I would like to draw attention to the bradyarrhythmia which follows long term treatment with digitalis it is possible that this bradyarrhythmia persisting in many subjects even after withdrawal of the drug may be the consequence of a chronic cardiotoxicity (delayed conduction at the level of A V node?)

The digitalis cardiac glycosides have some similarities to daunorubicin and adriamycin

The pathogenesis of anthracycline induced cardiomyopathy could be related to an intracellular overloading with calcium

As with daunorubicin and adriamycin the inhibition by digitalis compounds of membrane NA K ATPase increases the intracellular calcium concentration

One can therefore argue that this irreversible bradycardia which follows long term treatment with digitalis may result from permanent pharmacologic cardiomyopathy frequently unrecognized and mistreated

G F Levi M.D
4th Division of Medicine
Civilian Hospital
25100—Brescia
Italy

REFERENCES

1. Burch G E On the digoxin-diuretic cardiomyopathy AM HEART J 97 540 1979
2. Olson H L et al Electrolyte and morphologic alterations of myocardium in adriamycin treated rabbits Am J Pathol 77 439 1974

Proficiency and cost effectiveness in pediatric hospitals

To the Editor

This letter is written in response to the editorial entitled "The cost and benefits of segregation (by age)" by Dr Warren G Guntheroth which appeared in the May 1979 issue of the AMERICAN HEART JOURNAL (97 549 1979) In this editorial Dr Guntheroth suggests that The Guidelines for Pediatric Cardiology Diagnostic and Treatment Centers (Pediatrics 62 258-261) were written with a bias for pediatric hospitals.

The document that Dr Guntheroth refers to as Standards for pediatric cardiology diagnostic and treatment centers is in fact a *Guidelines* document It in no way addresses the effectiveness of children s hospitals versus general hospitals for the greater good of pediatric care

The document does address the importance of performing a minimal number of pediatric procedures in order to maintain proficiency in any unit It suggests that if children are to have cardiac catheterization or heart surgery a minimal number would need to be carried out in order to attain and maintain minimal proficiency and a degree of cost efficiency Some children s hospitals and some general hospitals have performed large numbers of cardiac catheterizations and surgical procedures in children and these have been the institutions pioneering many procedures which are now considered the ultimate ways of caring for children They have also trained some of the most respected pediatric cardiologists Other children s hospitals and many general hospitals are caring for few infants and children with heart disease and thus, cannot maintain adequate proficiency of physicians, nurses and paramedical personnel. In addition units admitting few patients cannot afford to develop specialized facilities such as pediatric cardiac catheterization laboratories, intensive care units, and ward facilities which meet the special needs of infants, children and adolescents. It is for this reason that the guidelines suggest that the same minimal number of infants and children be cared for in either a children s hospital or in a general hospital

The coordination of training of adult and pediatric cardiologists can occur in general hospitals handling children and adults or between children s hospitals and general hospitals where the good will of both the departments of internal medicine and pediatrics foster such behavior

All of the members of the Standards Committee have spent their professional careers in general hospitals with pediatric units To imply that the committee has developed self serving standards to perpetuate children s hospitals is a misreading of the content and intent of the guidelines

Standards Committee
Section of Pediatric Cardiology
American Academy of Pediatrics
Arno Hohn
Ira Gessner
Ronald M Lauer
Saul Robinson
Gerald Schiebler
George Emmanouilides (Chairman)
Dept. of Pediatrics
Harbor—U C.L A Medical Center
1000 W Carson St
Torrance Calif 90509

Reply

To the Editor

I appreciate the response of the Standards Committee to my Editorial, and knowing these Gentlemen well, I apologize for any implications that they personally were self serving On the other hand, I believe that an impartial reading of their "guidelines" will reveal at least a modest amount of "territo-

Table I Mean standard oxygen dissociation curve (n = 9) for human coronary sinus blood before and after nitroglycerin (NTG) (pH 7 4 pCO 40 mm Hg T 37° C)

Saturation SO %	*(A) PO mm Hg (+SD) before NTG*	*(B) PO mm Hg (+SD) 5 min after NTG*	*(A)-(B)*
5	5 4 (0 1)	5 6 (0 8)	-0 2
10	8 9 (1 0)	9 0 (0 7)	-0 1
20	14 1 (0 9)	14 1 (0 9)	-
30	18 2 (1 0)	18 1 (1 0)	+0 1
40	22 1 (1 2)	22 0 (1 2)	-0 1
50	26 1 (1.2)	26 0 (1 4)	+0 1
60	30 6 (1 4)	30 5 (1 7)	+0 1
70	36 2 (1 5)	36 1 (2 0)	+0 1
80	43 9 (1 7)	43 9 (2 5)	-
90	59 1 (2.5)	59 3 (4 0)	-0 2
95	79 0 (4 8)	79 8 (8 9)	-0 8
96	87 8 (6 3)	89 6 (8 9)	-1 8
97	9 9 (7 9)	106 1 (23 9)	-8.2
Hb g %	15 3 (1 0)	15 3 (1 0)	-
HbCO %	2 5 (1 0)	2 5 (1 0)	-
2 3 DPG $\left(\frac{\mu mole}{g\ Hb}\right)$	13 4 (2 4)	13 9 (2 1)	-0 5
Hct %	43 3 (2 7)	43 4 (2 7)	-0 1
MCHC %	35 3 (1 9)	35 3 (1 9)	-
Δ vol %	5 6 (0 7)	5 6 (0 7)	-

Age = 51 (±9) Smokers = 5 T test for paired data before and after NTG = NS + + +
Hb = hemoglobin HbCo = carboxyhemoglobin 2, 3 DPG = diphosphoglycerate Hct = hematocrit MCHC = mean corpuscular hemoglobin concentration Δ vol % = standard arteriovenous difference calculated in vol % between 60 and 35 mm Hg Po

imperative I am sure that we have no quarrel about the need for cost-effectiveness and good patient care particularly in a field where mistakes are apt to be fatal Of particular importance in relation to cost effectiveness the Standards Committee required of free standing pediatric hospitals a utilization of only 50% of that generally regarded as minimal for a general hospital Their letter implies that their primary purpose was efficiency of personnel However the assumption that supporting personnel will maintain proficiency only if patients are under some arbitrary age limit is without factual basis Similarly their letter and guidelines imply that bigger is better without evidence Although costs will clearly rise on a unit basis below some minimum number mortality and morbidity should serve as a more objective measurement of any program s right to be certified than an arbitrary number of cases under a given age I am aware of a major pediatric center in the East with poor surgical results in spite of a large caseload which subsequently improved dramatically when a cardiovascular surgeon (*not a* pediatric surgeon) was recruited I also disagree with the Committee s suggestion that innovations are directly related to caseload

If mortality and morbidity were used as an ongoing basis for certification centers doing only a handful of procedures would probably be eliminated rather quickly and assuredly they would be eliminated on a cost accounting basis Optimal care cost-effectiveness and good training *are* reasonable goals which can be shared by the public and most physicians I must reassert that segregation of children into free standing hospitals and segregation of cardiovascular training is not the best way

Warren G Guntheroth M.D
Department of Pediatrics
University of Washington School of Medicine
Seattle Wash 98195

Nitroglycerin and oxyhemoglobin dissociation curve of human coronary sinus blood

To the Editor

It has been shown in isolated dog heart preparations that nitroglycerin (NTG) significantly increased coronary venous Po and P_{50} the effect was observed three minutes after the start of the infusion The amount administrated (5 to 20 µg/minute) resulted in a blood concentration which was within the therapeutic dose range obtained in man The authors gave no satisfactory explanation for this phenomenon

We decided to confirm whether this effect was present or not in human subjects We studied nine male patients aged between 36 and 64 years in whom cardiac catheterization and coronary arteriography were performed for evaluation of chest pain suggestive of coronary disease seven had coronary artery disease one had cardiomyopathy and one had a normal coronary arteriogram

Blood was sampled in the coronary sinus before and five minutes after the administration of 1 mg NTG given sublingually The oxyhemoglobin dissociation curve (ODC) of the whole blood was determined at standard conditions (pH 7 4 temperature 37° C and Pco 40 mm Hg) with an apparatus constructed in this laboratory Hemoglobin and carboxyhemoglobin were measured by the IL-CO oximeter 282 hematocrit by microcentrifugation and diphosphoglycerate (2,3 DPG) by an enzymatic method (Sigma Kit)

The results are summarized in Table I The data clearly demonstrate that 1 mg NTG given sublingually inflences neither the slope nor the position of the whole ODC nor the level of the 2 3 DPG As we have previously observed that this drug had no effect on the same indices measured in the arterial blood it can be concluded at least for the concentration the method of administration employed and the type of patients investigated that NTG does not induce a rightward shift of the ODC and therefore does not enhance oxygen delivery to the heart muscle through this mechanism The discrepancy between our data and those of Warltier and associates is perhaps to be attributed to species differences.

Th Clerbaux Ph.D
M Rousseau M.D
B Nemery M.D
A Frans M.D
L Brasseur M D
University of Louvain
Cardiopulmonary Laboratory
FYCP-55 50
Avenue Hippocrate 55
B 1200 Brussels Belgium

REFERENCES

1 Warltier D C., Gross G J and Hardman H F Effect of right atrial pacing and nitroglycerin on myocardial oxygen balance Eur J Pharmacol. 34 299 19 5
2 Gross G J Warltier D C., and Hardman H F Effect of propranolol and nitroglycerin on hemoglobin-oxygen affinity Eur J Pharmacol. 36 267 1976
3 Clerbaux Th Fesler R and Bourgeois J A dynamic method for continuous recording of the whole blood oxyhemoglobin dissociation curve at constant temperature pH and pCO Med Lab Tech. 30 1 19 3
4 Fesler R., and Clerbaux Th Simple accurate solid state diode photometer for use in measuring oxygen saturation of whole blood Clin Chem 20 1135 1974
5 Sottiaux B Clerbaux Th Fesler R and Brohet C Computer processing of oxygen dissociation curves Comp Progr Biomed 6 178 19 6
6 Clerbaux Th Nemery B Brasseur L. and Frans A Nitroglycerin and blood oxygen dissociation curve of normal subjects Am Heart J 7 815 1979

Book reviews

Advances in Heart Disease Volume 2 By Dean T Mason New York 1978 Grune & Stratton Inc 552 pages Price $36 50

This issue on *Advances in Heart Disease* edited by Mason is concerned with eight topics advances in echocardiography nuclear cardiology ambulatory electrocardiography exercise testing exercise training and cardiac rehabilitation evasive evaluation of cardiac function pecial cardiovascular treatment and pecial cardiovascular topics. The many contributors present selected aspects of these eight topics most of which are confusing to the average physician who practices in the small towns and villages of the world These presentations fail to review critically each of these topics to indicate its more precise role in the care of patients outside of the large medical centers and large urban ho pitals The well trained clinicians of the small towns and rural areas of the world who treat most of the sick need to realize that they are not handicapped when they fail to have immediate access to these special procedures These procedures should be available only when indicated but they are rarely if ever indicated e g nuclear cardiology Regardless of the opinion of this reviewer the book does present in satisfactory fashion in one volume recent advances in these special fields for the reader who does not follow closely the cardiologic literature The clinician who reads these advances carefully and critically can determine for himself how well he employs these special and costly procedures and can also learn how well he practices cardiology with or without dependence on them

Cerebral Circulation and Stroke By Lawrence C McHenry Jr St. Louis, Mo 1978 Warren H Green Inc 280 pages Price $22 50

This is a practical small concise book on an important problem in medicine The book includes chapters on history atomy physiology diagnosis and management of stroke e illustrations are good but not very clear These could be improved. The book is highly recommended to all medical students, housestaff and internists as well as to family physicians. The correlation of central nervous system anatomy with the arterial blood supply is a good feature of the book Physicians with a busy schedule will find the book very good and useful

British Heart Journal Prevention of Arrhythmias Proceedings of a Symposium Arran ed by Professor D G Julian London 1978 British Medical Association 98 pages Price $3.50

This a supplement of the *British Heart Journal* consists of the papers presented at a sympo ium held at Newcastle upon Tyne during September 1977 The 98 pages include 14 presentations concerning conduction tissues effect of cardiac denervation ventricular arrest catecholamine effects surgical treatment of ventricular tachycardia a pects of electrophysiology action of antiarrhythmic drugs management of ventricular fibrillation and other arrhythmic problems in coronary artery disease and use of drugs in preventing sudden death There is really nothing new in this publication However the supplement provides a single source of information of considerable interest to cardiologists This is a good publication

Cardiomyopathy Associated with Systemic Myopathy Genetic Defect of Actomyosin Influencing Muscular Structure and Function By Franz Buchner Shunzo Onishi, and Akira Wada Baltimore 1978 Urban & Schwarzenberg Medical Publishers 99 pages Price $18 50

This small book on cardiomyopathy is devoted to an excellent model for the study of myocardial and systemic myopathy The B Osaka hamster with a genetic myopathy provides an extremely useful source of material for research ers The authors describe very vividly the clinical and pathologic manifestations of Bajuz Myopathy Surely these ick hamsters are of considerable value to clinical and laboratory research However this reviewer cannot avoid being "touched with sympathy and pity for these hamsters as the clinical manifestations of the disease unfold This book is worth reading by everyone physicians, researchers, and laymen to learn how these unfortunate animals suffer and contribute their lives and genetic background to I hope benefit mankind The clinical course of the disease is well described and the manifestations of congestive heart failure are clearly presented Man already owes much to these little hamsters

The Sinus Node Structure Function and Clinical Relevance Edited by Felix I M Bonke The Hague Netherlands 1978 Martinus Nijhoff 459 pages. Price 105 guilders

This book contains the papers presented at a workshop in the Netherlands during July 1977 The many papers review thoroughly many aspects of the function of the sinus node Interest in the normal pacemaker of the heart cannot be over-emphasized Much of the discussions are well known to those who follow the medical literature closely but this book collects in one volume a fairly extensive review of the SA node function and disturbances in function with disease and treatment This is a good clear source of important information

Modern Electrocardiography Edited by Z Antaloczy Amsterdam The Netherland –Oxford 1978, Excerpta Medica 567 pages, Price $77 50

This book contains the proceedings of the Fourth International Congress on Electrocardiography held in Hungary in September 1977 The many papers are brief and reflect very well the opinions of the authors This reviewer shall not attempt to indicate differences related to data presented such as that on page 407 where the term "primary" T wave change related to the ventricular gradient was reported in the literature prior to 1969 Yet the author indicated this term was first reported in 1969 Some presentations are so brief that only the well informed electrocardiographer" can understand adequately the implications Unfortunately symposia these days are not sufficiently critical of data presented Those interested in experimental electrocardiography can find the present state of research and thinking in electrocardiography in this book. Clinicians in busy practice of medicine will find the book of some but limited use There certainly is a need to evaluate extensively and critically the applications and limitations of many ECG procedures such as Holter monitoring treadmill monitoring His bundle electrocardiographic recordings etc The performance of ECG recorders needs critical review also The recorders in general use have very poor fidelity

Circulatory Diseases of the Limbs A Primer By David I Abramson New York, 1978, Grune & Stratton Inc 367 pages Price $19 00

Abramson has written a small concise and clear "primer on circulatory diseases of the limbs The author has devoted his medical career to peripheral vascular diseases and is

certainly capable of producing an authoritative book on the subject for clinicians The book is intended for doctors It is clinically oriented and is written so that physicians in practice without sophisticated apparatus can manage peripheral vascular diseases very well *The chapters on history taking* and physical examination are clearly written for clinicians and obviously written by one without extensive clinical experience The lack of attention to peripheral vascular diseases in recent years in spite of the magnitude of the problem reflects the value and need for this book This is a good book for all physicians Its value can be even more appreciated by those *who are already in the field of peripheral vascular disease and* especially by physicians well informed of the physiology pharmacology and pathophysiology of the blood vessels and lymphatics

Mechanisms of Vasodilatation Edited by P M Vanhoutte Wilrijk and I Leusen Gent Basel, Switzerland 1978 S Karger Medical and Scientific Publishers 307 pages Price $53 50

This symposium on mechanisms of vasodilatation should interest all physicians physiologists and pharmacologists The many papers are concerned with intrinsic factors related to vascular smooth muscle relaxation local and humoral events, vasodilator agents used in clinical practice neurogenic vasodilatation and general remarks The papers are short but succinct Much of the material presented is quite old indicating an increased need for greater interest and research in the peripheral circulation The importance of vasodilation and the behavior of vascular smooth muscle is obvious The regulation of blood flow to the most vital organs of the body as well as to the limbs is dependent upon vascular smooth muscle This is a good book

Books received

Medical Physics Vol 1 By A C Damask New York 1978 Academic Press Inc 374 pages Price $26 00

Physiology of Membrane Disorders Edited by Thomas E Andreoli Joseph F Hoffman and Darrell D Fanestil, New York 1978 Plenum Publishing Corp 1 122 pages Price $75 00

Geochemistry and the Environment Volume III The National Research Council Washington D C., 1978 National Academy of Sciences 200 pages.

The American Way of Life Need Not be Hazardous to Your Health By John W Farquhar M D New York, 1978 W W Norton & Company 195 pages Price $9.95

Teaching Film on the Failing Heart

Eli Lilly and Company is pleased to announce the availability of a new medical teaching film "The Failing Heart Role of Inotropic Agents in Its Management

Produced in consultation with R Joe Noble M D F A C C the 25 minute film explains the physiology of the normal and failing heart the role of calcium at the intracellular level and the role of inotropic agents in correcting the pathophysiology The film is available on loan from the Lilly Educational Resources Library 565 Fifth Avenue New York N Y 10017 For further information including purchase write Eli Lilly and Company Box 100B Indianapolis Indiana 46206

Postgraduate Course on Heart Disease

The University of Arizona Health Sciences Center Tucson announces its annual postgraduate educaton course entitled "Clinical Recognition and Management of Heart Disease to be held on March 27 through 29 1980 in Tucson Arizona The course is sponsored by the American College of Physicians registration information can be obtained from the Registrar's Office of the American College of Physicians or contact Gordon A Ewy M D Professor of Medicine Course Director University of Arizona Health Sciences Center Tucson Ariz 85724

The International Society and Federation of Cardiology (ISFC)

The International Society and Federation of Cardiology (ISFC) combines scientific teaching and research with further education. Its Scientific Board and the Public Education Committee are respectively in charge of these activities and collaborate closely The Scientific Councils organize multinational research studies teaching seminars and postgraduate courses and also set up task forces on proposed international classifications and definitions of arrhythmias ischemic heart disease cardiomyopathies and hemodynamics Important new developments in cardiology are also the target of special committees The Public Education Committee attempts to educate the public in matters of preventive medicine and holds workshops and conferences Hypertension was covered in 1979 and plans for additional workshops for 1980 to emphasize the cardiovascular dangers of cigarette smoking are being made Another major function of the ISFC is to sponsor the World Congresses of Cardiology which are held every four years The ISFC carries out its program in close liaison with the World Health Organization

Further information may be obtained from the ISFC P O Box 117 1211 Geneva 12 Switzerland

American Heart Journal

April 1980 Volume 99 Number 4

Editorial

Duplicity in a Committee Report on Diet and Coronary Heart Disease

Kurt A Oster M D

Fairfield Conn

The advice of scientific committeemen frequently arrived at by consensus has profoundly influenced the dietary habits of Americans over the past 20 years The validity of such advice needs examination from time to time

The fourth report of the American Heart Association Committee on Nutrition appeared in the October 1978 issue of *Circulation* It is worth while to test this report for its logic epistemology and philosophy by an unbiased research of the cited references The Committee has stated using standard methods for diet and coronary disea e assessment no population habitually subsisting on a low fat and cholesterol diet or one that is low in saturated fats and cholesterol has an appreciable amount of coronary disease By extrapolation they suggest a diet high in saturated fat and/or cholesterol is an important factor for a high incidence of coronary heart di ease

This inference is not logical it is specious To establish a causal relationship it must be shown that all population groups with high saturated fat and cholesterol intake al o exhibit a high incidence of atherosclerosis This is decidedly not the case with the French the Eskimos and the Masai all populations consuming diets high in saturated fat

Further the so called standard method for diet assessment are notoriously inaccurate and a reliable method for assessing coronary disease morbidity in large population groups is nonexistent As for mortality the gross inaccuracies arising from the use of death certificate data for cardiovascular-renal diseases are well known

The high saturated fat consumption of the French people and their relatively low incidence of atherosclerosis have been noted by Keys and Keys who attempted to forestall negative criticism of their study by stating that French physicians underdiagno e coronary heart disease

The three allegedly favorable results of the early diet trials cited by the Committee do not provide sufficient evidence for any responsible scientist schooled in scrutinizing experimental data and reconciling them with public relations inspired propaganda These trials were objectively analyzed by Davis and Havlik in Rifkind and Levy s Hyperlipidemia Diagno is and Therapy They concluded the Los Angeles Veterans Administration Study failed to provide convincing proof of the lipid hypothesis Analysis of the Finnish Diet Study data raised doubts about the validity and generalizability of the results In the O lo Diet-Heart Study if total CHD mortality is considered including both fatal myocardial infarction and all sudden deaths combined the results are not statistically significant

Such critical and unbiased negative evaluations of these diet-heart studies diff nsid

From th Dep rtm B l gy F irfi ld Un rsity Fairfield Conn

Rec ed f publ M 1 19 9

R pri t req est ku A Ost M D 951 Lafa ette B vd Bridgeport C nn 06€ 1

from the positive assessments of the AHA Nutrition Committee and also from that of Hegsted in his most recent defense of the dietary goals which he helped prepare. The speciousness of the aforementioned trials for serum cholesterol lowering has been demonstrated. In objective science one expects to be shown not only positive findings but also negative results of legitimate trials. Such failures have been omitted from the report of the Nutrition Committee.

John S. Mill might have anticipated the so-called McGovern Report when he wrote in 1856: "Not the violent conflict between parts of the truth but the quiet suppression of half of it is the formidable evil. There is always hope when people are forced to listen to both sides. It is when they attend to only one that errors harden into prejudice and truth ceases to have the effect of truth."

The Minnesota Coronary Survey attempted to prevent CHD with a diet which consisted partially of 38 per cent fat with a polyunsaturated-saturated ratio of 1.6 and 166 mg of cholesterol. Of these 9,449 subjects the treated group did attain a 14 per cent decrease of serum cholesterol but during 4.5 years of total follow-up there were no significant differences in the number of myocardial infarctions, sudden deaths or strokes when all ages of men and women were combined. In men less than 50 years of age a favorable treatment effect was seen although the numbers were not large enough to achieve statistical significance. Yet according to Framingham Study statistics a 14 per cent reduction in serum cholesterol should have effected a 28 to 35 per cent decrease in CHD incidence.

With this critical examination of the cited "positive evidence" which is in reality negative, one can only conclude that the Nutrition Committee has presented spurious claims of accomplishment to the uninitiated physician who may lack the time and training to evaluate the original findings for himself. The psychological motivation for the Committee's self-serving deception is not clear.

In a June 1978 article the same AHA Nutrition Committee admitted [illegible] that there is no unequivocal scientific basis for the recommendation to lower serum cholesterol in the entire population and that it should be left to the judgment of the individual physician to advise such a diet to his patients. "A reasoned resolution of the controversy is not currently possible."

C. J. Glueck, a member of the Nutrition Committee, concluded in an article in *Drug Therapy*, October 1978, the same publication time as that of the Committee report: "Since there is no unequivocal evidence regarding the effects and efficacy of dietary alteration in the most hypercholesterolemic group of children, this question undoubtedly will remain controversial." The Committee is so inconsistent one doubts its validity.

Contrary to Dr. Glueck's downplaying of the potential for harm inherent in the dietary recommendations, there is definite experimental and clinical suspicion that such an unnatural diet designed to lower serum cholesterol and consisting of up to 10 per cent polyunsaturated fatty acids (PUFA) may well have deleterious effects over time. In fact investigators at the University of Maryland have reported on carcinogenicity caused by trans-unsaturated fatty acids contained in many margarine products.[1]

A much quoted authority on the "alternate diet," W. E. Connor, has warned about PUFA: "Possible harmful effects of ingesting large amounts of polyunsaturated vegetable fat include enhanced formation of cholesterol gallstones, a stimulus to carcinogenesis, increased vitamin E requirements, promotion of obesity, increased uptake of plant sterols, and possible increased cholesterol absorption. In a long-term clinical trial the incidence of gallstones in autopsied individuals whose long-term diet had contained a large amount of polyunsaturated fat was significantly increased over a control group. The threat of enhanced carcinogenesis still must be considered, perhaps in part because of accumulation of peroxides or perhaps because a sudden increase in dietary polyunsaturated fat might provide an unusual stimulus for carcinogenesis."

Contrary to the statement of the AHA researchers that the Mediterranean diet is the same as their recommended one, I know of no

To gain [illegible] and to attain [illegible] the group has misrepresented references. In 19[illegible] the American Medical Association Council on Food and Nutrition and the Food and Nutrition Board of the National Academy of Sciences National Research Council restricted the dietary recommendations to individuals falling into risk categories on the basis of their plasma lipid levels and did not extend them to the entire population starting in childhood as [illegible] in the AHA report.

population group which consumes fats in the proposed proportions of 10 per cent saturated 10 per cent monounsaturated and up to 10 percent polyunsaturated fatty acids Keys[11] reported a maximum consumption of only 7 percent polyunsaturated fatty acids which he extrapolated from his studies of very limited population groups in seven countries However there are certainly many populations which consume saturated fats in amounts similar to that of North Americans but which have one third or less the CHD that is present in the United States The lower prevalence of CHD in European population groups where all known risk factors are identical to those of North Americans has been reported by Keys He is seeking the presence in Americans of another as yet undiscovered risk factor X

One of the major completed trials the Coronary Drug Project was successful in lowering serum cholesterol but was an abysmal failure in its intended purpose–to demonstrate that a significant reduction of serum cholesterol will diminish the risk for recurrent myocardial infarction However sometimes a dogma is so strongly entrenched that no disappointing adverse experimental results can dispel it Wenger admitted without reservation in a paper delivered at the 1977 A H A meeting in Miami that the drugs employed in the Coronary Drug Project were without any beneficial effect Still she has faith that appropriate diets in a healthy population would accomplish what the drugs had failed to do in a deseased group of CHD sufferers[1] To quote the philosopher Sir Karl R Popper Every theory can be immunized against criticism If we allow such immunization then every theory becomes unfalsifiable What elevates science over pseudo science is the scientific method of finding true secure and justifiable knowledge

The 1978 A H A Committee Report mentioned for the first time the beneficial significance of cholesterol sequestered in high density lipoproteins (HDL) The three previous A H A statements dated 1965 revised 1968 and 1973 (*not* four as stated in the A H A Committee Report) made no note of this important finding The prior committees were convinced of the completeness of their data but they forgot that the beneficial effects of HDL were reported as early as 1951 Which known facts have been overlooked in 1978 by the group of A H A members forming the Nutrition Committee of this year?

I have tried to show that the evidence of undesirable high lipid levels of typical American men and women lies in the eyes of the beholder Blackburn[6] has termed this condition mass hyperlipidemia This seems to be a newly invented epidemiological disease in search of a human body The analogy of the benefit of reduction of elevated blood sugar in diabetic subjects which can be construed from studying the Nutrition Committee report cannot be applied to the reduction of allegedly elevated lipid levels in some atherosclerotic subjects until the minimum requirements of safety and efficacy of the recommendations have been proven We should not be lured into dramatic action simply for the sake of *doing something* in the undeniable presence of a problem Though they may sound very impressive vague dietary recommendations have very little likelihood of curbing the epidemic of atherosclerotic diseases

People have hailed what appears to be a substantial reduction of the cardiovascular disease death rate from a 1950 peak of 804 3 per hundred thousand for persons aged 55 to 64 to a low of 626 in 1973[1] suggesting that the decrease was a natural consequence of eating the right kind of fats

Considering that the first A H A statement on fats was published in 1965 and granting a lead time of approximately 20 years from the inception of atherosclerosis to its clinical manifestation and eventual death it is indeed difficult to attribute the drop in death rate to greater consumption of polyunsaturated vegetable oils

To base recommendations for every American on untried unproven unsubstantiated data endangers not only the health of those Americans but also the future of medicine s credibility We physicians unlike the politicians cannot afford the luxury of having a revised second edition in December 1977 of dietary goals which were thought to be the last word ten months before in February 1977 An editorial in *Lancet*[1] may serve as a warning against overstressing the significance of correlations and multiple regressions used as source material for the A H.A report Correlation and regression analysis of international differences in mortality against a wide variety of dietary social and economic variables has a depressing history It began with

and repeatedly turns to the enthusiastic interpretation of a few points purporting to represent the diets and coronary disease of millions of people of diverse backgrounds The assertions of causality on the basis of such evidence have been at times extreme But give a man three weapons—correlation regression and a pen—and he will use all three

Summary

The most recent American Heart Association Committee on Nutrition Report Diet and Coronary Heart Disease is examined for the applicability of its quoted references It is concluded that the A H A advised diet which includes 10 per cent saturated fats 10 per cent monounsaturated fats and up to 10 per cent polyunsaturated fats should not be recommended for use by all Americans There are serious unresolved questions concerning the expected benefits and the potential risks of such a glut of polyunsaturated oils for life long use There is no known large population group that consumes a diet up to 10 per cent of which is polyunsaturated oils

REFERENCES

1 Bierman E L *Chairman* Corwin R D Farquhar J W Geer J C Glueck C J Grundy S M Insull W Koller L H and Winston M (A H A Nutrition Committee 19" 19 8) Diet and coronary heart disease Circulation 58 19 8 (Suppl)
2 Rose G A and Blackburn H Cardiovascular Survey Methods Geneva 1968 World Health Organization p 0
3 Moriyama I M Baum W S Haenszel W M and Mattison B F Inquiry into diagnostic evidence supporting medical certifications of death Am J Publ Health 48 13 6 1958
4 Keys A and Keys, M How To Eat Well and Stay Well the Mediterranean Way Garden City New York 19 5 Doubleday & Co Inc Appendix p 467 Table 9
5 Rifkind B M and Levy R I eds Hyperlipidemia Diagnosis and Therapy New York 1977 Grune & Stratton Inc
6 Hegsted D M Dietary goals a progressive view Am J Clin Nutr 31 1504 1978
7 Oster K A Prevention of atherosclerosis fact or fiction? Med Counterpoint Apr 1979
8 Glueck C J Mattson F and Bierman E L Diet and coronary disease N Engl J Med 298 1471 19 8
9 Glueck C J and Stein E A Managing children with hyperlipidemias Drug Therapy Oct 19 8 pp 117 1?6
10 Enig M G Munn R J and Keeney M Dietary fat and cancer trends A critique Fed Proc 37 2215 19 8
11 Keys A ed Coronary heart disease in seven countries American Heart Association Monograph 29 Circulation 41 1970 (Suppl)
12 Tibblin G, Keys A, and Werko L eds Preventive Cardiology New York 1972 John Wiley & Sons
13 Stamler J Forman S and Krol W F Natural history of myocardial infarction in the Coronary Drug Project long term prognostic importance of serum lipid levels, Am J Cardiol 42 489 1978
14 Wenger N K The Coronary Drug Project implication for clinical care Circulation 55 and 56 113 1977 (Suppl)
15 Schilpp P A ed The philosophy of Karl Popper LaSalle Ill 1974 The Library of Living Philosophers, vol 14 1 2
16 Blackburn H Diet and mass hyperlipidemia public health considerations, in Diet Related to Killer Diseases VI Appendix Washington D C, U S Government Printing Office July 26 1977 pp 101 140
17 National Center for Health Statistics Vital Statistics of the United States vol II Mortality selected years, 1975
18 Editorial The anomaly that wouldn t go away Lancet 2 978 Nov 4 1978

Clinical communications

R wave amplitude changes during stress testing Comparison with ST segment depression and angiographic correlation

Lorenzo de Caprio
Sergio Cuomo
Paolo Bellotti
Bruna Adamo
Maurizio Postiglione
Carlo Vigorito
Franco Rengo
Naples Italy

A reduction of R wave amplitude was found during exercise stress testing in normal subjects In patients with coronary artery disease (CAD) an increase or no variations of R wave at all were observed

Left ventricular volumes decrease in healthy subjects during exercise while in patients with CAD these volumes remain unchanged

According to the observation of Brody who postulated that the intracavitary blood mass affects the QRS amplitude other authors have suggested that the exercise induced R wave amplitude changes may represent a useful index for detecting CAD

In order to evaluate the usefulness of R wave amplitude changes (ΔR) in the screening of patients with CAD we compared the sensitivity specificity and predictive accuracy of the ΔR method with the standard ST segment depression and we tried to find a correlation between ΔR and findings at coronary arteriography and left ventriculography

From the Istituto di Patologia Speciale Medica e Metodologia Clinica 2 Facoltà di Medicina e Chirurgia dell Università di Napoli.

Received for publication June 12 1979
Accepted for publication Oct. 16 1979

Reprint requests Dr Lorenzo de Caprio Istituto di Patologia Medica Facoltà di Medicina Via S Pansini 80131 Naples, Italy

Materials and methods

Exercise stress tests records and coronary angiograms of 107 patients referred for evaluation of chest pain were reviewed retrospectively

The patients were divided in the following groups The normal group was composed of 36 subjects 29 males and seven females 34 to 60 years old none of whom had coronary artery narrowing or abnormal left ventricular wall motion (0 V) The CAD group was composed of 71 patients with angiographic evidence of stenosis of 70% in one or more major coronary arteries

These patients were divided into three groups The first group was composed of 16 patients having one vessel disease (1 V) there were 12 males and four females between 33 and 61 years old Four (25%) of these had electrocardiographic evidence of an old myocardial infarction five (31%) of the 16 had an abnormal left ventricular contraction pattern

The second group was composed of 31 patients having two vessel disease (2 V) there were 26 males and five females between 35 and 67 years old Fourteen (45%) of these 31 had electrocardiographic evidence of an old myocardial infarction 22 (71%) of the 31 demonstrated an abnormal left ventricular contraction pattern

The third group consisted of 24 patients with three vessel disease (3 V) there were 22 males

Table I True negative and false positive results using ST and ΔR in 36 patients without angio graphic evidence of CAD (zero vessel disease group N = 36)

	ST	*ΔR*
TN	28 (78)	19 (53%)
FP	8 (22)	17 (47%)

P < 0[illegible] versus ST
TN = true negative FP = false positive

Table II Predictive accuracy sensitivity and specificity of ΔR and ST standards

	ΔR	*ST*
Predictive accuracy	78%	86%
Sensitivity	83%	75%
Specificity	53%	78%

P < 0[illegible]

and 2 females with ages ranging from 42 to 71 years old Fourteen (58%) of these showed electro cardiographic evidence of an old myocardial infarction and 20 (83%) of the 24 demonstrated angiographic evidence of abnormal left ventricu lar wall motion

Patients underwent a progressive maximal exercise stress test using the maximal predicted heart rate as a target end point Exercise testing was performed in a thermostatically controlled room (20° C) using a SASME Ergo 2 bicycle ergometer All drugs were discontinued at least 48 hours before the exercise test The patients started cycling in the sitting position with a 50 watt load which was increased by 20 watts every two minutes

Exercise was stopped either because of chest pain or ST segment depression of 2 mm below the resting level Electrocardiographic leads CM 4 5 and 6 were monitored continuously (Avionics 3000 model)

Significant ST segment depression was defined as 1 mm ST depression below the resting level 60 msec from the J point if the depression was horizontal or flat and 1 5 mm depression 80 msec from the J point if the depression was upsloping The measurements of ST segment depression were made in the CM 5 lead in the immediate postexercise period

Electrocardiographic recordings were obtained at rest every minute during exercise in the

Table III True positive and false negative results using ST and ΔR in 71 CAD patients (CAD group n = 71)

	ST	*ΔR*
TP	53 (75%)	59 (83%)
FN	18 (25%)	12 (17%)

TP = true positive FN = false negative

immediate postexercise period and every minute during the first 5 minutes of recovery

R wave amplitude change was measured in millimeters from the isoelectric line to the peak of the R wave in CM 5 lead for at least 10 consecu tive beats The average value was used to mini mize respiratory variations ΔR was measured comparing R wave amplitude at rest and immedi ately at the end of the exercise As previously de scribed we considered ΔR values equal or greater than zero to be significant for CAD Stress test records were evaluated in each group using ST segment depression and R wave amplitude changes

Specificity sensitivity and predictive accuracy for each method were calculated and compared Statistical analysis was performed using the Fish er exact test ' Stress testing was evaluated with out prior knowledge of the angiographic results

Coronary angiograms were performed using the Sones technique' and were recorded on 35 mm film in multiple projections Left ventriculogra phy was performed in the right anterior oblique projection

A luminal stenosis of one or more major coro nary arteries equal to or greater than 70% was considered significant for CAD The left ventricu lar angiograms were divided into five segments (1) posterobasal (2) diaphragmatic (3) apical (4) anterolateral and (5) anterobasal Areas with an abnormal contraction pattern were described qualitatively as hypokinetic when systolic move ment was less than normal akinetic when no movement was observed during systole and dys kinetic when paradoxical systolic movement was seen The angiograms were evaluated without prior knowledge of the stress test results

The stress test results and angiographic record were examined by two independent observers

Patients with cardiac valvular disease cardio myopathy conduction defects premature ven tricular complexes or hypertensive cardiova cu

Table IV True positive and false negative results using ST and ΔR criteria in one two and three coronary vessel disease patients

	ST		*ΔR*	
	TP	*FN*	*TP*	*FN*
1 V (n = 16)	11 (69%)	5 (31%)	10 (63%)	6 (37%)
2 V (n = 31)	22 (71%)	9 (29%)	27 (87%)	4 (13%)
3 V (n = 24)	20 (83%)	4 (17%)	22 (92%)	2 (8%)

1 V = one vessel disease 2 V = two vessel disease 3-V = three vessel disease TP = true positive FN = false negati

Table V Electrocardiographic results of stress testing in one vessel disease patients with abnormal and normal left ventricular wall motion using ΔR criteria

	$\uparrow\Delta R$	$-\Delta R$	$\downarrow\Delta R$
1 V patients (n = 16)	7 (44%)	3 (19%)	6 (37%)
A.W M (n = 5) (31%)	2 (40%)	2 (40%)	1 (20%)
N W M (n = 11) (69%)	5 (45.5%)	1 (9%)	5 (45.5%)

1 V = one vessel coronary disease A W M = abnormal left ventricular wall motion N W M = normal l ft ntricular wall motion

Table VI Electrocardiographic results of stress testing in two vessel coronary disease patients with abnormal and normal left ventricular wall motion using ΔR criteria

	$\uparrow\Delta R$	$-\Delta R$	$\downarrow\Delta R$
2 V patients (n = 31)	21 (68%)	6 (19%)	4 (13%)
A.W M (n = 22) (71%)	19 (86%)	2 (9%)	1 (5%)
N W M (n = 9) (29%)	2 (22%)	4 (45%)	3 (33%)

V = two vessel oronary dise se A W M = abnormal left ventricular w ll mot on N W M = normal left v ntricular wall motion.

lar disease and those taking digitalis or beta adrenergic blocking drugs were excluded

Results

Comparison between ΔR and ST segment depression Twenty eight (78%) of the 36 patients *in the O V group had a true negative response* during stress testing using the ST depression standard while only 19 (53%) of the 36 showed true negative results the using ΔR method (Table I) The specificity of the ST method was significantly ($P <$ 02) greater than ΔR (Table II)

Fifty three patients (75%) of the 71 of the CAD group were true positives by the ST standard using ΔR the true positive results increased to 59 patients (83%) however this increase of sensitivity was not statistically significant (Tables II and III)

The predictive accuracy of the two methods employed was similar (Table II)

As shown in Table IV both criteria produced similar results in patients with one vessel disease However the ΔR method showed better results in the 2 V and 3 V patients than ST segment depression

Correlation between ΔR and angiocardiographic findings The R wave increased in seven (44%) of the 16 patients with one vessel disease it remained unchanged in three (19%) and decreased in six (37%) (Table V) Eleven patients of the 1 V group had normal left ventriculography ΔR was equal to or greater than zero in six (54%) and was lower than zero in five (46%) In the five patients of the 1 V group with abnormal left ventricular wall motion ΔR was equal to or greater than zero in four (80%) and lower than zero in one (20%) (Table V)

Twenty one patients (68%) of the 31 with two vessel disease had an increase of R wave amplitude six patients (19%) had no change and four (13%) had a decrease (Table VI) Twenty two patients in the 2 V group demonstrated abnormal left ventricular wall motion 21 (95%) of these had ΔR values equal to or greater than zero and only one (5%) showed ΔR values lower than zero Nine patients of the 31 of the 2 V group demonstrated a normal left ventriculographic pattern six (67%) of the nine had ΔR values equal to or greater than zero while *three (33%) showed ΔR values lower* than zero (Table VI)

Seventeen patients (71%) and five patients (21%) out of 24 of the 3 V group had an increase or no change of the ΔR wave amplitude respectively only two (8%) of the 24 showed a decrease of the R wave (Table VII) Twenty patients of 24 in the 3 V group showed abnormal left ventricular wall motion 19 (95%) of the 20 had ΔR values equal to or greater than zero while one (5%) showed a decreased R wave amplitude Only four patients of the 24 of the 3 V group demonstrated normal left ventricular contraction pattern three (75%) of the four had ΔR values greater than zero and one (25%) had a decreased R wave amplitude (Table VII)

The percentage of R wave *abnormal* results

Table VII Electrocardiographic results of stress testing in three vessel coronary disease patients with abnormal and normal left ventricular wall motion using ΔR criteria

	↑ΔR	−ΔR	↓ΔR
3 V patients (n = 24)	17 (71%)	5 (21%)	2 (8%)
A W M (n = 20) (83%)	14 (70%)	5 (25%)	1 (5%)
N W M (n = 4) (17%)	3 (75%)	—	1 (25%)

3-V = three vessel coronary disease A W M = abnormal left ventricular wall motion N W M = normal left ventricular wall motion

Table VIII Incidence of abnormal left ventricular wall motion in one two and three vessel coronary disease patients and of ΔR values ≥ 0 in zero vessel subjects and in one two and three vessel coronary disease patients*

	ΔR ≥ 0	A W M
0 V	19/36 (53%)	—
1 V	10/16 (63%)	5/16 (31%)
2 V	27/31 (87%)	22/31 (71%)‡
3-V	22/24 (92%)†	20/24 (83%)§

*Statistical analysis performed by Fisher exact test
†P < 03 versus 1 V
‡P < 01 versus 1 V
§P < 0002 versus 1 V
1 V = one vessel coronary disease 2 V = two vessel coronary disease 3 V = three vessel coronary disease 0-V = zero vessel coronary disease A W M = abnormal left ventricular wall motion

was significantly higher (P = 03) in three vessel disease as compared with one vessel disease patients There was no significant difference between the normal group and the single vessel disease group The two vessel disease patients showed a higher percentage of ΔR abnormal results as compared to the single vessel disease patients this difference exhibited a borderline P value (P = 06) (Table VIII)

In the 2 V and 3 V groups abnormal left ventricular wall motion was found more frequently than in the 1 V group (P < 01 and P < 002 respectively) (Table VIII)

Discussion

Recent reports have suggested that exercise induced R wave amplitude changes may be a useful index for detecting CAD Bonoris and associates obtained these results in a population with a large number of false positive and negative responses using the ST segment depression method However we believe that such findings can be influenced by the purposely introduced large number of false negative and false positive results

Therefore the purpose of our study is to establish if R wave amplitude changes can be used as a screening method for detecting patients with CAD when compared with more reliable ST segment depression results and also if the ΔR standard can be related to the angiographic severity of CAD

Increased sympathetic activity during stress testing is responsible for a reduction in left ventricular volumes in normal subjects [1] Further reports have supported the evidence that the R wave amplitude is related to the left ventricular blood volume [1] Therefore the reduced QRS amplitude during an exercise stress test is likely to be related to the reduction of the left ventricular volume

On the other hand in patients with CAD the R wave amplitude increases or does not change at all such findings are likely to be related to the left ventricular impairment during exercise in these patients [1] Indeed cardiac volume increases during atrial pacing or exercise induced angina [1, 11] moreover myocardial ischemia causes or worsens left ventricular impairment [1, 21]

Our results are consistent with those of other authors who found a correlation between ΔR values equal to or greater than zero during stress testing and the severity of CAD The patients with single vessel disease showing the lowest incidence of abnormal left ventriculograms demonstrated the lowest percentage of ΔR values equal to or greater than zero during the exercise stress test The patients with double and triple vessel disease showing left ventricular contraction abnormalities very frequently demonstrated a ΔR value equal to or greater than zero Indeed 92% of the patients in the 3 V group had an increased or unchanged R wave amplitude the highest percentage recorded in our series However we must emphasize the limitations in the ΔR evaluation of stress testing As previously described by other authors the ST segment depression is well correlated with CAD the sensitivity of this method ranges from 80% to 55% and its specificity ranges from 80% to 90% Our results agree with these values We found that the R wave method is more sensitive than ST segment depression but the latter is significantly more specific than the former

It has been reported that the false negative

results are more common in less severe CAD [3,13] our results show that the R wave amplitude changes as well as ST segment depression have a comparable incidence of false negative results in patients with single vessel disease

Only 53% of the patients in the 0 V group have ΔR lower than zero during stress testing our results agree with those of Gillespie and colleagues[34] who demonstrated the high sensitivity but also the low specificity of the ΔR method

Other authors found abnormal R wave changes during stress testing in about 10% of young subjects without any clinical evidence of CAD and with a negative stress test using the ST method The mechanism responsible for such an increase of the R wave amplitude in healthy subjects is unknown

On the other hand R wave amplitude may decrease even in patients with CAD if the hyper contractility of the normal areas of myocardium counterbalances the effects of diseased areas We believe that while such a mechanism could be effective in less severe CAD patterns it is unlikely to be effective in patients with severe CAD and left ventricular impairment bearing in mind that the left ventricular performance is further impaired during myocardial ischemia [3]

These controversial results indicate that the analysis of the R wave changes during exercise stress testing might necessitate further research To attribute them to the functional impairment is not entirely satisfactory It is likely that the left ventricular impairment during exercise is a very important determinant but other factors could also play a role

In conclusion it is true that the R wave amplitude often increases during stress testing in patients with CAD and this increase is very likely related to the more severe angiographic CAD pattern Thus the ΔR method improves the sensitivity of exercise stress testing however this is accompanied by a concomitant reduced specificity Therefore we consider that the usefulness of the ΔR method remains to be determined

Summary

One hundred and seven exercise stress tests and coronary angiograms were reviewed retrospectively in order to evaluate the usefulness of R wave amplitude changes (ΔR) during exercise compared with ST segment depression in the screening of patients with coronary artery disease (CAD)

We also attempted to correlate ΔR with the severity of CAD as expressed by coronary arteriography and left ventriculography

Thirty six patients showed no coronary artery narrowing (0 V) the remaining 71 patients with stenosis of 70% of at least one of the major coronary arteries were divided into three groups

Sixteen patients had single vessel disease (1 V) five (31%) in this group showed abnormal left ventricular wall motion Thirty one patients had two vessel disease (2 V) 22 (71%) of the 31 demonstrated abnormal left ventricular wall motion Twenty four patients had three vessel disease (3 V) 20 (83%) of the 24 showed abnormal left ventricular wall motion

We considered ΔR values ≥ 0 and ST segment depression ≥ 1 mm significant for diagnosis of CAD

The sensitivity of the ΔR method in predicting CAD was superior to the method based upon ST segment depression however the latter was significantly ($P < 02$) more specific than the former The predictive accuracy of these two criteria was similar

We found ΔR values ≥ 0 more frequently in the 2 V and 3 V groups as compared with the 1 V group Patients of the 2 V and 3 V groups had a significantly higher incidence of abnormal left ventricular wall motion ($P < 01$ $P < 0002$ respectively) in comparison with 1 V patients Thus ΔR values ≥ 0 during exercise stress testing are very likely related to left ventricular impairment

Even though the accuracy of the ΔR method was greater in more severe CAD it seems to be offset by a concomitant decrease in specificity

REFERENCES

1 Simonson E Effect of moderate exercise on the electrocardiogram in healthy young and middle-aged man J Appl Physiol 5 584 1953
2 Lloyd Thomas H C The effect of exercise on the electrocardiogram in healthy subjects Br Heart J 23 260 1961
3 Simoons M L and Hugenholtz P G Gradual changes of the ECG wave form during and after exercise normal subjects Circulation 52 5 0 19 5
4 Lloyd Thomas H G The exercise electrocardiogram patients with cardiac pain Br Heart J 23 561 1961
5 Kentala E, and Luurila O Response of R amplitude of postural changes and to exercise A st on healthy subjects and patients surviving acute dial infarction Ann Clin Res 7 258 1975
6 Ellestad M H Stress testir ... les and P Philadelphia 19 5 F A D ... pages & Bonoro P E Greenberg P ... anet

Table VII Electrocardiographic results of stress testing in three vessel coronary disease patients with abnormal and normal left ventricular wall motion using ΔR criteria

	↑ΔR	–ΔR	↓ΔR
3 V patients (n = 24)	17 (71%)	5 (21%)	2 (8%)
A W M (n = 20) (83%)	14 (70%)	5 (25%)	1 (5%)
N W M (n = 4) (17%)	3 (75%)	–	1 (25%)

3-V = three vessel coronary disease A.W.M = abnormal left ventricular wall motion N.W.M = normal left ventricular wall motion

Table VIII Incidence of abnormal left ventricular wall motion in one two and three vessel coronary disease patients and of ΔR values ≥ 0 in zero vessel subjects and in one two and three vessel coronary disease patients*

	ΔR ≥ 0	A W M
0 V	19/36 (53%)	–
1 V	10/16 (63%)	5/16 (31%)
2 V	27/31 (87%)	22/31 (71%)‡
3-V	22/24 (92%)†	20/24 (83%)§

*Statistical analysis performed by Fisher exact test
†P < .03 versus 1 V
‡P < .01 versus 1 V
§P < .002 versus 1 V
1 V = one vessel coronary disease 2 V = two vessel coronary disease 3-V = three vessel coronary disease 0 V = zero vessel coronary disease A.W.M = abnormal left ventricular wall motion

was significantly higher (P = .03) in three vessel disease as compared with one vessel disease patients There was no significant difference between the normal group and the single vessel disease group The two vessel disease patients showed a higher percentage of ΔR abnormal results as compared to the single vessel disease patients this difference exhibited a borderline P value (P = .06) (Table VIII)

In the 2 V and 3 V groups abnormal left ventricular wall motion was found more frequently than in the 1 V group (P < .01 and P < .002 respectively) (Table VIII)

Discussion

Recent reports have suggested that exercise induced R wave amplitude changes may be a useful index for detecting CAD Bonoris and associates obtained these results in a population with a large number of false positive and negative responses using the ST segment depression method However we believe that such findings can be influenced by the purposely introduced large number of false negative and false positive results

Therefore the purpose of our study is to establish if R wave amplitude changes can be used as a screening method for detecting patients with CAD when compared with more reliable ST segment depression results and also if the ΔR standard can be related to the angiographic severity of CAD

Increased sympathetic activity during stress testing is responsible for a reduction in left ventricular volumes in normal subjects Further reports have supported the evidence that the R wave amplitude is related to the left ventricular blood volume Therefore the reduced QRS amplitude during an exercise stress test is likely to be related to the reduction of the left ventricular volume

On the other hand in patients with CAD the R wave amplitude increases or does not change at all such findings are likely to be related to the left ventricular impairment during exercise in these patients Indeed cardiac volume increases during atrial pacing or exercise induced angina[11] moreover, myocardial ischemia causes or worsens left ventricular impairment[23]

Our results are consistent with those of other authors who found a correlation between ΔR values equal to or greater than zero during stress testing and the severity of CAD The patients with single vessel disease showing the lowest incidence of abnormal left ventriculograms demonstrated the lowest percentage of ΔR values equal to or greater than zero during the exercise stress test The patients with double and triple vessel disease showing left ventricular contraction abnormalities very frequently demonstrated a ΔR value equal to or greater than zero Indeed 92% of the patients in the 3 V group had an increased or unchanged R wave amplitude the highest percentage recorded in our series However we must emphasize the limitations in the ΔR evaluation of stress testing As previously described by other authors the ST segment depression is well correlated with CAD the sensitivity of this method ranges from 80% to 55% and its specificity ranges from 80% to 90% Our results agree with these values We found that the R wave method is more sensitive than ST segment depression but the latter is significantly more specific than the former

It has been reported that the false negative

The natural history of aortic stenosis in adults

Michael A Chizner M D *
David L Pearle M D **
Antonio C deLeon Jr M D ***
Washington D C

Information on the natural history of valvular aortic stenosis in adults is essential in their proper mangement Previous studies of such cases diag nosed on clinical and postmortem findings sug gest poor prognosis with the onset of angina syncope and congestive heart failure A subse quent study involving a small number of cases with hemodynamic confirmation tends to support this premise[s] Since aortic valve surgery devel oped simultaneously with cardiac catheterization techniques most patients subsequently diag nosed as having significant aortic stenosis have been selected for valvuloplasty or valve replace ment Therefore natural history data in aortic stenosis are based on a small number of hemody namically studied patients and large series are unlikely to be reported in the future The present study provides a unique opportunity for long term follow up of 42 adults with hemodynamic documentation of isolated valvular aortic steno sis

Methods

Forty two consecutive adults aged 20 years or older with isolated valvular aortic stenosis seen initially at Georgetown University Hospital between 1966 and 1971 were identified All had hemodynamic confirmation of the diagnosis and for various reasons did not undergo early surgical intervention Cases with associated moderate or severe aortic insufficiency or mitral valvular dis ease were excluded Thirty two patients were symptomatic and ten were asymptomatic at the time of initial clinical assessment and cardiac catheterization The hemodynamic severity of aortic stenosis was defined according to the fol lowing parameters

1 Mild aortic stenosis Aortic valve area (AVA) greater than 1 1 cm and/or a systolic peak to peak gradient less than 40 mm Hg

2 Moderate aortic stenosis Aortic valve area (AVA) of 0 71 to 1 09 cm and systolic peak to peak gradient of less than 70 mm Hg

3 Severe aortic stenosis Aortic valve area of 0 7 cm or less and/or a systolic peak to peak gradient of greater than 70 mm Hg

Patients in the moderate and severe categories both met previously described criteria for signif icant stenosis [s] All patients had a history and physical examination by two or more members of the cardiology division The precatheterization assessment included a phonocardiogram cardiac series and a 12 lead electrocardiogram Left ven tricular hypertrophy (LVH) was identified according to the electrocardiographic criteria of Sokolow and Lyon Aortic valve calcification was determined by chest x ray or fluoroscopy A mortality curve for symptomatic patients with hemodynamically moderate or severe stenosis was constructed by regression analysis to obtain a line of best fit [1]

Results

A Symptomatic aortic stenosis Thirty two patients were symptomatic at the time of cardiac

From th D isio of Cardi logy Georg town Uni rsity Med cal Center Washingt D C

S pport d in part by gra t from the Metr pol tan H rt Guild and th Be jamin M Memorial Fund

Rec ed f p blicat n July 17 19 9

Acc pted for publ t on Dec 3 1979

Reprint request D d L P arle M.D Georg t wn Uni ersity Hosp tal 3800 Reservoir R d N W Wa hington D C 000

Fellow in C rd l gy Dept of Med ci e Geo g town Uni ers ty H pital

Ass t nt P ofessor of M d cin D pt of Med cine Ge g town Uni ersity Hospit l

Professor f Med ine D pt of Med in Geo g town Un ersity Hosp t l

000 8 03/80/040419 + 06$00 f0/0 © 1980 The C V Mosby Co

Table I Symptomatic moderate aortic stenosis

Pt	Age/sex	Mos from onset to cath			Peak to peak gradient (mm Hg)	LVEDP (mm Hg)	AVA (cm)	Status (time from cath to follow up)	
		Angina	Syncope	CHF					
G B	62 M	1	0	12	20	8	0 90	Died age 6?	(? months)
W B	55 M	0	0	12	34	—	0.90	Alive	(?6 months)
T F	61 M	36	0	12	54	24	—	Died age 61	(? days)
B F	61 M	0	0	84	29	32	—	Died age 62	(1 month)
L H	46 M	0	6	12	47	10	0.80	AVR	(64 months)
R R	60 M	96	0	0	71	15	0 90	AVR	(33 months)
R Z	49 M	1	1	0	38	12	0 80	Died age 50	(8 months)
J S	52 M	0	2	2	41	3	1 13	Died age 53	(?? months)
E M	62 M	0	0	3	37	13	0 90	Died age 64	(?? months)
C H	22 M	0	0	60	57	5	0.80	Alive	(80 months)

Table II Symptomatic severe aortic stenosis

Pt	Age/sex	Mos from onset to cath			Peak to peak gradient (mm Hg)	LVEDP (mm Hg)	AVA (cm)	Status (time from cath to follow up)	
		Angina	Syncope	CHF					
W B	56 M	0	0	12	150	24	0 35	Died age 56	(6 months)
F C	58 M	12	0	60	87	33	—	Alive	(61 months)
C H	63 F	12	1	12	120	21	0 44	Died age 63	(3 days)
J J	60 M	0	2	4	100	11	—	Died age 60	(9 days)
J L	72 M	0	12	0	65	31	0.50	Died age 69	(12 months)
J M	59 F	12	0	12	35	6	0 60	Alive	(114 months)
C M	44 M	9	9	9	99	30	—	Died age 44	(? weeks)
M M	64 F	6	6	6	98	18	0 40	Died age 64	(1 month)
D R	48 M	0	0	4	88	18	0 40	Died age 48	(3 month)
K R	53 F	0	0	6	88	40	0.20	Died age 53	(1 month)
I S	62 M	6	0	0	87	25	0 50	Died age 65	(33 months)
R Z	7? F	0	2	84	65	4	0.50	Died age 7?	(2 months)
R F	40 M	24	24	24	80	18	0 90	AVR	(?3 months)

catheterization Thirteen had severe 10 had moderate and nine had mild aortic stenosis Patients in the moderate and severe groups are listed in Tables I and II with selected clinical hemodynamic and follow up data Survivors in these groups were followed from 26 to 114 months (average 64 4 months) from the time of catheterization

Ten of the 13 patients with severe six of the 10 with moderate and four of the nine with mild stenosis were dead by the end of the follow up period Fig 1 represents a mortality curve from the onset of the first symptom from those patients in the moderate and severe categories Data points are corrected for the number of patients followed for each time period e g only 17 of the 23 patients were followed for a total of 11 years Twenty six per cent were dead by one year after the first symptom 48% by two years 57% by three years 64% by five years 80% by eight years and 94% by eleven years

Table III shows the prevalence and duration of symptoms for patients with moderate and severe aortic stenosis Congestive heart failure was the most common symptom (83%) Although the average survival was shorter in patients with syncope no symptom carried a significantly worse prognosis because of the wide variability in duration of survival Symptoms of congestive heart failure for example were present in two patients (one with moderate one with severe stenosis) for eight years before death Among surviving patients one with a gradient of 84 mm Hg and left ventricular end diastolic pressure (LVEDP) of 33 mm Hg had symptoms of congestive failure for over eight years

Although the mortality rate was somewhat greater in patients with severe (77%) than in those

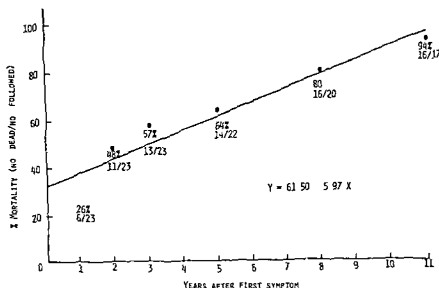


Fig 1 Mortality curve for symptomatic patients with moderate and severe aortic stenosis A line of best fit is constructed by regression analysis

Table III Duration of symptoms in patients with significant aortic stenosis

Symptom	*No with symptom/ no of symptomatic patients*	*No dead/no with symptom*	*Duration of Symptoms (months—onset to death)*
Angina	11/23 (48%)	7/11 (64%)	3 39 Mean 16 43 ± SD 14 67 (SE 5 55)
Syncope	10/23 (44%)	8/10 (80%)	2 34 Mean 10 ± SD 9 13 (SE 3 23)
CHF	19/23 (83%)	13/19 (68%)	4 36 Mean 23 85 ± SD 28 11 (SE 7 80)

with moderate stenosis (60%) the difference was not significant Survival within the moderate and severe groups was also plotted against peak to peak gradient aortic valve area and left ventricular end diastolic pressure While patients with higher left ventricular end diastolic pressures had somewhat higher mortality rates no significant differences were observed

Of the 16 patients with moderate or severe aortic stenosis who died eight died suddenly without reaching a hospital Four died with progressive congestive failure two died with myocardial infarction and cardiogenic shock (which occurred three days after catheterization in one patient) One patient reached the hospital in a comatose condition and in pulmonary edema after a syncopal episode The mode of death is unknown in one patient

Four of the ten patients in the mild category were dead by the end of the follow up period All four had histories of congestive heart failure and three had histories of angina

B Asymptomatic aortic stenosis Eight patients (Table IV) in the moderate and severe groups were asymptomatic at the time of cardiac catheterization and three have not had subsequent aortic valve surgery These patients have survived for periods ranging from 29 to 84 months (average 59 7 months) and remain asymptomatic Of note all these patients are less than 30 years old The other five patients were asymptomatic at the time of catheterization but have subsequently had aortic valve replacement because of the onset of symptoms after surviving an average of 75 8 months (20 to 139 months) These patients also were less than 30 years old

Discussion

Symptomatic aortic stenosis It is a widely held clinical view that symptomatic hemody

Table IV Asymptomatic patients with significant aortic stenosis

Patient	*Age at Cath (yrs)*	*Category*	*Peak to peak gradient (mm Hg)*	*Follow up after cath (months)*	*Interval between cath & AVR (months)*
R B	24	Severe	72	84	–
S C	22	Severe	59	–	139
W D	25	Moderate	58	29	–
R Y	20	Moderate	50	66	–
L R	22	Moderate	53	–	78
N G	29	Severe	100	–	75
L K	29	Severe	75	–	20
R H	22	Moderate	64	–	114

namically significant aortic stenosis carries a poor prognosis[11,12] The prognosis for the 23 symptomatic patients with moderate or severe stenosis in our study was somewhat worse than in those previously reported[8] Forty eight % were dead two years after the onset of the first symptom 64% had died by five years and 94% had died by eleven years (percentages are corrected for the number of patients followed) The worse prognosis in our study compared to that of Frank Johnson and Ross[8] may be explained by our exclusion for separate consideration of patients asymptomatic at the time of cardiac catheterization who appear to have a lower mortality rate

Among those patients with symptomatic hemodynamically significant aortic stenosis no subgroup at higher risk could be identified Although congestive heart failure was the most common symptom and syncope presaged the shortest average survival no symptom carried a significantly worse prognosis Patients with severe stenosis had a slightly worse but not significantly different prognosis than those in the moderate group with ten of 13 patients (77%) dead by the time of follow up versus six of ten dead (60%) in the moderate category Higher left ventricular end diastolic pressure carried a slightly worse prognosis but did not clearly separate survivors from those who died

It is striking that those patients classified as having mild aortic stenosis also demonstrated a very high mortality rate with four of nine (44%) of these patients dead by the end of the follow up period This result probably reflects the presence of associated myocardial disease of other etiology (one had a documented acute myocardial infarction and another had calcified coronary arteries) rather than the aortic valve lesion alone Since coronary arteriograms were not performed on these patients this conclusion is speculative However, coronary artery disease associated with aortic valve disease in the older patient is common[13,17] Its presence is not necessarily predictable by the presence or absence of angina pectoris[15,17] In one large series 58% of those with significant aortic stenosis and angina pectoris had angiographically documented coronary artery disease of those with aortic stenosis without angina 26% had coronary artery disease[15]

Of the 16 patients in the moderate and severe groups who died eight died within hours of manifesting new symptoms without reaching a hospital and another died shortly after arriving in a hospital emergency ward in a comatose condition and with pulmonary edema after a syncopal episode All these patients were symptomatic before death This result confirms the accepted frequency of sudden death in symptomatic aortic stenosis and represents a higher incidence than the 15 to 20% previously reported[1,3,11]

Our data demonstrate that symptomatic hemodynamically severe or moderate aortic stenosis carries a very high mortality Survival is significantly less than that reported in patients undergoing aortic valve replacement for aortic stenosis[18,2] Surgery is therefore indicated for these patient

Asymptomatic aortic stenosis Patients with moderate or severe aortic stenosis who are without symptoms pose a special therapeutic problem to the clinician One hesitates to subject an asymptomatic patient to a surgical intervention which carries a significant mortality rate[1,2] However there is always the concern that without surgery the patient is at risk of sudden death Moreover it can be argued that delaying surgery may lead to myocardial deterioration which could

increase operative mortality and compromise the long term results of aortic valve surgery

There are considerable data on the risk of sudden death in children with congenital aortic stenosis This risk has been placed as high as four % per year for the first three decades[21] but the subgroups at risk can be identified with some assurance It has been said that patients less than 20 years old with congenital aortic stenosis who die suddenly are symptomatic and/or demonstrate a left ventricular strain pattern by electrocardiogram and that the incidence of sudden death in a child without symptoms or a left ventricular strain pattern is almost nil However the recent Joint Study on the Natural History of Congenital Heart Defects followed a large group of children—most of whom had mild aortic stenosis—and identified three patients who died suddenly all with significant aortic stenosis One of these a 16 year old child did not demonstrate a left ventricular strain pattern Therefore the absence of such a pattern cannot be considered a guarantee against the risk of sudden death

The risk of sudden death in asymptomatic adults with hemodynamically significant aortic stenosis is less well established It can certainly occur One of three such patients (a 45 year old male) reported by Frank Johnson and Ross died suddenly In summarizing data from retrospective studies without hemodynamic confirmation Ross and Braunwald state that only three to five percent of the deaths in acquired aortic stenosis appear to occur suddenly in patients without symptoms " However these data are derived from patients dying suddenly and the authors assess the patients symptomatic status retrospectively They do not quantitate the risk of sudden death or the prognosis of the asymptomatic patient with significant aortic stenosis

Eight of our patients with moderate or severe aortic stenosis were asymptomatic at the time of catheterization These patients were not typical of the study population in that all were less than 30 years old when catheterized All had murmurs detected in childhood and presumably had congenital aortic stenosis Five of the eight had left ventricular strain by electrocardiogram Of the eight patients three subsequently developed symptoms (all three with congestive heart failure angina in two) and underwent aortic valve replacement Five are alive without surgery at the end of the follow up period (four remaining asymptomatic) None of the eight asymptomatic patients therefore experienced sudden death in a follow up period averaging 69 8 months

These data are of course limited both in the number and in the unrepresentative nature of the adult patients involved However along with the studies previously cited they suggest that while sudden death can occur in asymptomatic adult patients with severe aortic stenosis it is uncommon and thus not a paramount indication for aortic valve surgery Therefore the decision to replace the aortic valve in these patients depends on a clinical judgment weighing the small risk of sudden death before the development of symptoms (which clearly warrant surgery) against the morbidity and mortality of valve replacement and life with a prosthetic valve

Summary

Accepted clinical views about the natural history of aortic stenosis are based on surprisingly little hemodynamically documented data and further information in unlikely to be forthcoming in the modern surgical era Therefore follow up data were obtained on 42 adult patients with isolated valvular aortic stenosis catheterized at Georgetown University Hospital who did not undergo early valve replacement

Of 32 symptomatic patients 23 had moderate or severe stenosis and were followed until death or for an average of 64 4 months after catheterization The prognosis was more ominous than previously reported Mortality rates from onset of symptoms were 26% at one year 48% at two years and 57% at three years Fifty six % of deaths occurred suddenly within hours of new symptoms

Asymptomatic patients with moderate or severe stenosis did not share the high mortality rate of those with symptoms Eight such patients were followed for an average of 69 8 months and none died

REFERENCES

1 Bergeron J Abelmann W H Vasquez Milan H and Ellis L B Aortic stenosis—clinical manifestations and course of the disease—review of 100 proved cases Arch Intern Med 94 911 1954

2 Wood P Aortic stenosis Am. J Cardiol 1 553 1958

3 Mitchell A M Sackett C H Hunzicker W J, and Levine S A The clinical features of aortic stenosis Am Heart J 48 684 1954

4 Kumpe C W and Bean W B Aortic stenosis Medicine 27 139 1948
5 Takeda J Warren R and Holzman D Prognosis of aortic stenosis Arch Surg (Chicago) 87 931 1963
6 Braunwald F and Morrow A G Obstruction to left ventricular outflow Current criteria for the selection of patients for operation Am J Cardiol 12 53 1963
7 Ross J Jr and Braunwald F Aortic stenosis Circulation 37 and 38 (Suppl V) 61 1968
8 Frank S Johnson A and Ross J Jr Natural history of valvular aortic stenosis Br Heart J 35 41 1973
9 Sokolow M and Lyon J P The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads AM HEART J 37 161 1949
10 Dixon W R and Massey T J Jr Introduction to Statistical Analysis 3rd ed New York 1969 McGraw Hill Book Company
11 Crawley I S Morris D C and Silverman B D Valvular heart disease chapter 60B *in* The Heart Hurst J W Logue R B Schlant R C Wenger N K eds New York 1978 McGraw Hill Book Company
12 Rapaport E Natural history of aortic and mitral valve disease Am J Cardiol 35 221 1975
13 Nakib A Lillehei C W and Edwards J E The degree of coronary atherosclerosis in aortic valvular disease Arch Pathol 80 517 1965
14 Harris C N Kaplan M A Parker D P Dunne E F Cowell H S and Ellestad M H Aortic stenosis angina and coronary artery disease interrelations Br Heart J 37 656 1975
15 Lewis R C and Creus A I Angina pectoris and aortic valve disease Cardiovasc Clin 7 169 1975
16 Basta L L Raines D Najjar S and Kioschos J M Clinical hemodynamic and coronary angiographic correlates of angina pectoris in patients with severe aortic valve disease Br Heart J 37 150 1975
17 Moraski R F Russell R O Jr and Rackley C E Aortic stenosis angina pectoris and coronary artery disease (Abstract) Circulation 50(Suppl III) 4 1974
18 Starr A Grunkemeier G L Lambert L E Thomas D R Sugimura S and Lefrak E L Aortic valve replacement A ten year follow up of non cloth covered caged ball prostheses Circulation 56(Suppl II) 133 1977
19 Copeland J G Griepp R B Stinson E B and Shumway N E Long term follow up after isolated aortic valve replacement J Thorac Cardiovasc Surg 74 875 1977
20 Richardson J V Kouchoukos N T Wright J O III and Karp R B Combined aortic valve replacement and myocardial revascularization results in 220 patients Circulation 59 75 1979
21 Barnhorst D A Oxman H A Connolly D C Pluth J R Danielson G K Wallace R B and McGoon D C Isolated replacement of the aortic valve with the Starr Edwards prosthesis a nine year review J Thorac Cardiovasc Surg 70 113 1975
22 Bjork V O Henze A and Holmgren A Long term results with Bjork Shiley tilting disc valve in aortic valvular disease Israel J Med Sci 11 161 1975
23 Campbell M The natural history of congenital aortic stenosis Br Heart J 30 514 1968
24 Nadas A S and Fyler D C Pediatric Cardiology 3rd ed Philadelphia 1972 W B Saunders Company p 481
25 Wagner H R Ellison R C Keane J F Humphries J O and Nadas A S Clinical course in aortic stenosis Circulation 56(Suppl I) 17 1977

ail aortic valve leaflets M-mode and two-mensional echocardiographic manifestations

nine Krivokapich M D *
hn S Child M D *
avid J Shorton M D **
s Angeles Calif

udden disruption of aortic valve integrity results acute severe aortic insufficiency (AI) The athophysiology, clinical recognition and management of this life threatening syndrome has een thoroughly reviewed by Morganroth and ssociates Flail ruptured and prolapsing are all escriptors applied to the disrupted aortic valve he most common etiology is infective endocardis (IE) other causes include myxomatous degeneration aortic root dissection and traumatic upture

Echocardiography provides an invaluable non nvasive means of rapidly evaluating patients with AI in an attempt to determine the etiology nd severity of their lesion Vegetations are suggested by shaggy fuzzy nonuniform or dense echoes associated with an aortic valve that has normal motion Premature mitral valve closure correlates with severe aortic insufficiency and usually indicates imminent need for aortic valve replacement High frequency diastolic aortic valve flutter and echoes extending from the aortic valve into the left ventricular outflow tract (LVOT) in diastole are M mode echocardiographic features used to identify a flail aortic leaflet It has been noted however that these LVOT echoes may be seen with aortic valve vegetations without actual leaflet disruption [1] Two dimensional echocardiography (2 D echo) permits visualization of the aortic valve and the LVOT simultaneously Four patients with anatomic documentation of flail aortic valves are presented with M mode and 2 D echocardiograms illustrating the utility of both studies in diagnosing a flail aortic leaflet

Methods and patients

Four patients admitted to the UCLA Center for the Health Sciences with the clinical syndrome of severe aortic insufficiency were evaluated with M mode and 2 D echocardiography

M mode echocardiograms were performed in the standard manner [3] on a Smith Kline Instrument (SKI) Ekoline 20A Ultrasonoscope with a 2.25 MHz transducer focused at 10 cm Recordings were made by a Honeywell 1856 A strip chart recorder on Kodak light sensitive paper

Cross sectional echocardiograms (2 D) were performed with a commercially available mechanical two-dimensional imaging system (SKI Ekosector I) utilizing a 30 degree or wide angle (83 degree) transducer head The 30 degree angle provided better image quality and structural detail whereas the wide angle was useful for spatial orientation The standard long axis (LAX) and short axis (SAX) views were obtained in all patients and when technically possible a four chamber apical (hemiaxial) view was also done Images were recorded on video tape via a Sanyo VTC 1000 cassette recorder for analyses in real time slow motion and single frame format Individual frames were photographed using a Polaroid system These pictures are presented in

From th Di is o f Card l gy Department of Medicine School of Medici U ers ty of Calif rnia–Los Angeles.

Recei ed fo publi at n A g 19 9

A epted f publicat n Dec 19 1979

Reprint req est J n n Krivok pich, M D Di isi n f C rdiology UCLA Ce ter fo th Health Scien es, Los A g les Cal f 900 4

Assistant Professo of Medicin UCLA C t f r th Health Sc ences.

Cardi logy F llow UCLA Ce te fo th H lth Scie ces.

0002-8703/80/0404-5 + 13$01.30/0 © 1980 The C V Mosby Co

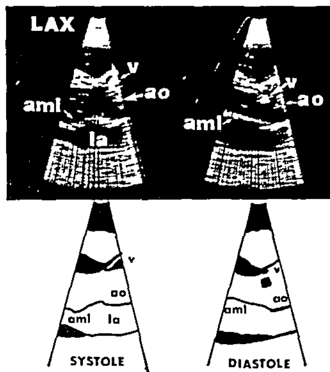


Fig 1 Two dimensional echocardiogram (LAX) in systole and diastole from Case 1 prior to clinical decompensation The apex is to the left of the figure A bulky vegetation is noted on the right coronary cusp which moves with the leaflet in systole and diastole No portion of the leaflet and/or the vegetation extends below the level of the aortic ring Abbreviations *aml* anterior mitral leaflet *ao* = aorta *la* = left atrium *LAX* = long axis view *v* = vegetation

the text however the still photos result in a loss of detail and the inability to appreciate motion Therefore the important added information gained from the viewing of real time 2 D echocardiograms cannot adequately be illustrated in this text

Case reports

Case 1 A 31 year old white male presented with a three week history of fevers chills fatigue weight loss arthralgias and skin lesions He denied knowledge of a murmur rheumatic fever or a history of intravenous drug abuse but underwent dental work two months previously

The physical examination revealed aortic insufficiency with no evidence of heart failure The clinical diagnosis of aortic valve infective endocarditis was made and the patient was begun on intravenous antibiotics with improvement in symptoms

The M mode echocardiogram revealed multiple echoes on the right coronary cusp compatible with valvular thickening and/or vegetations There was diastolic mitral valve fluttering consistent with aortic insufficiency The left ventricular end diastolic dimension was 60 mm with increased interventricular septal excursion suggesting left ventricular volume overload A two dimensional study confirmed these findings (Fig 1)

Two weeks after admission blood cultures grew *Kingella kingae* After four weeks of intravenous penicillin he was discharged to home on two weeks of oral penicillin Six weeks after discharge he again presented with fatigue and noted orthopnea and palpitations

M mode echocardiography revealed that his left ventricular end diastolic dimension had increased to 70 mm and the left atrium had increased to 40 mm The echoes consistent with aortic leaflet vegetations persisted in the aortic root but there were also extra diastolic echoes in the left ventricular outflow tract consistent with prolapse of an aortic leaflet or part of a vegetation (Fig 2) The mitral valve closed almost completely prior to a very small a wave suggesting increased left ventricular diastolic pressure due to severe aortic insufficiency The two dimensional study demonstrated an arc like movement of a portion of the aortic valve into the left ventricular outflow tract during diastole with the anterior aortic wall serving as the hinge point of the motion (Fig 3) This was a distinct change from the previous studies

Based on the above findings he was felt to have disrupted at least one aortic leaflet leading to severe aortic insufficiency and acute heart failure Appropriate cultures were taken and penicillin was restarted He underwent a porcine heterograft aortic valve replacement 36 hours after admission without having a left sided cardiac catheterization At surgery a trileaflet aortic valve was found a portion of which appeared to prolapse into the left ventricular outflow tract All three leaflets were somewhat thickened The right cusp was covered with multiple friable polypoid appearing vegetations a second leaflet was perforated and the third was torn (Fig 4) Organisms were seen in the vegetation but cultures yielded no growth He had an uneventful postoperative course and has clinically done well

Case 2 A 28 year old black male first became aware that he had the murmur of aortic insufficiency when he presented at age 26 with paroxy

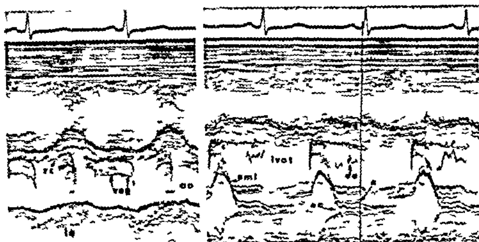


Fig 2 M mode echocardiograms from Case 1 after clinical decompensation The aortic root tracing on the left illustrates the shaggy fuzzy echoes of a vegetation(s) on the aortic valve which are best seen in diastole *On the right tracing* left ventricular outflow tract extra echoes above the mitral valve imply the prolapse of a portion of the aortic valve and/or a vegetation into the left ventricle Mitral valve closure effectively occurs at *ec* significantly before the QRS although a small a wave is noted This is consistent with severe aortic insufficiency Abbreviations *a* = a wave *aml* = anterior mitral leaflet *ao* = aorta *ec* = early closure *ee* = extra echoes *ivs* = interventricular septum *la* = left atrium *lvot* = left ventricular outflow tract *rc* = right aortic cusp *veg* = vegetation

mal atrial tachycardia He had no history of rheumatic fever or drug abuse and the aortic valve lesion was felt most likely to be congenital in origin One year later his heart was enlarged on chest x ray and digoxin and furosemide were begun

Over the next year he noted increasing dyspnea on exertion orthopnea occasional paroxysmal nocturnal dyspnea chest and left shoulder pain with heavy exertion increasing fatigability and occasional palpitations He was admitted to the UCLA Medical Center for elective cardiac catheterization

Physical examination revealed a blood pressure of 115/70 mm Hg with bounding arterial pulses There was no evidence of congestive heart failure The heart was enlarged Auscultation revealed a 2/6 mid systolic murmur at the base and a long 2/6 coarse impure decrescendo diastolic murmur which began with the second heart sound and was heard along the left sternal border and at the apex where it developed a rumbling quality A fourth heart sound was present at the lower sternal border

M mode echocardiography demonstrated a dilated left ventricle of 70 mm at end diastole with increased septal excursion consistent with left ventricular volume overload The left atrium was slightly dilated at 41 mm There was fluttering of the posterior mitral valve leaflet and premature mitral valve closure suggesting severe aortic insufficiency In addition aortic valve diastolic fluttering suggested a flail aortic cusp (Fig 5) Two dimensional echocardiography revealed diastolic extension of aortic valve tissue into the left ventricular outflow tract (Fig 6) Vegetations were not noted on the M mode or on 2 D echocardiograms The above findings were diagnostic of a flail aortic valve

Cardiac catheterization revealed a pulmonary capillary wedge pressure of 15 mm Hg with a left ventricular end diastolic pressure that varied from 30 to 50 mm Hg The aorta was normal in size and three aortic cusps were visible There was 4+ aortic insufficiency

The patient underwent elective aortic valve replacement with a Starr Edward valve At surgery a trileaflet aortic valve was found with intact commissures and no evidence of vegetations The noncoronary cusp was redundant and prolapsed into the left ventricular outflow tract Microscopic examination of the valve revealed diffuse myxomatous changes The immediate postoperative course was complicated only by pericarditis which responded to indomethacin

Case 3 A 3o year old black female heroin abuser was transferred to UCLA for management of progressive heart failure secondary to Group D

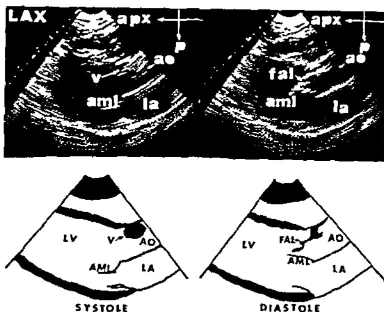


Fig 3 Two-dimensional echocardiogram (LAX) in systole and diastole from Case 1 after clinical decompensation In systole the aortic leaflets and vegetation are seen only in the aortic root During diastole the flail portion of an aortic cusp extends into the left ventricular outflow tract almost contacting the anterior mitral leaflet The dynamic nature of the arc inscribed by the leaflet in moving from aortic root into the left ventricular outflow tract with the anterior aortic wall as its hinge point is impossible to appreciate in these stopframe pictures. Abbreviations *aml* = anterior mitral leaflet *ao* = aorta *apx* = apex *fal* = flail aortic leaflet *la* = left atrium *LAX* = long axis view *p* = posterior *v* = vegetation



Fig 4 Surgically removed aortic valve from Case 1 The top cusp was extremely thickened and covered with vegetations The tear in one leaflet and the perforation of the remaining leaflet can easily be appreciated

streptococcus (Enterococcus) endocarditis after two weeks of antibiotic therapy On admission she was lethargic and tachypneic sitting upright in bed with a blood pressure of 120 40 mm Hg Jugular vein pulsations were not seen There were no rales on chest examination Cardiac examination revealed an enlarged heart with a slight right ventricular impulse felt at the left sternal border The first heart sound intensity was decreased

There was a 3/6 midsystolic crescendo decrescendo murmur at the left and right upper sternal borders with radiation to the carotids a high pitched 3/6 systolic murmur at the apex with radiation into the axilla and a 3/6 high pitched diastolic murmur which began with the second sound and extended through most of diastole The liver was 12 cm by percussion and was nonpulsatile There was minimal peripheral edema and no peripheral stigmata of infective endocarditis (IE)

Chest x ray demonstrated a markedly enlarg heart with evidence of left and right atri enlargement and upper lobe pulmonary venou distension Swan Ganz catheterization revealed pulmonary wedge pressure of 40 mm Hg wit large V waves present consistent with signi cant mitral regurgitation Mean right atrial pres sure exceeded 20 mm Hg The cardiac output wa 2 0 liters per minute The patient was believed t have severe aortic regurgitation secondary t enterococcal bacterial endocarditis with mitra and tricuspid regurgitation The etiology of th mitral regurgitation was unclear possibly repre senting organic disease secondary to vegetations The tricuspid regurgitation was thought to b functional

M mode echocardiography revealed multipl

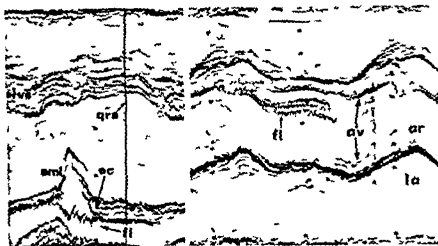


Fig 5 M mode echocardiograms from Case 2 On the *left tracing* fluttering of the posterior leaflet of the mitral valve is noted consistent with aortic insufficiency The *straight black line* denotes the beginning of the QRS complex The closure point *(ec)* of the mitral valve occurs early (i e before the QRS) and is consistent with severe aortic insufficiency The *right tracing* illustrating the aortic root demonstrates high frequency aortic diastolic echoes suggesting a flail aortic cusp Abbreviations *aml* = anterior mitral leaflet *av* = aortic valve leaflets *ar* = aortic root *ec* = early closure *fl* = flutter *ivs* = interventricular septum *la* = left atrium *qrs* = beginning of QRS complex

systolic and diastolic echoes in the aortic root consistent with vegetations (Fig 7) There was marked diastolic fluttering of the aortic valve in diastole as well as chaotic systolic fluttering both of which strongly suggested a flail aortic leaflet Extraneous diastolic echoes present in the left ventricular outflow tract further suggested the diagnosis of a flail aortic leaflet although the presence of a prolapsing vegetation was also possible Fluttering of the mitral valve in diastole with premature mitral valve closure consistent with severe aortic insufficiency was also present No definite mitral valve vegetations were noted (Fig 8) The left ventricular end diastolic dimension of 61 mm with increased left ventricular wall excursion suggested left ventricular volume overload The left atrium was enlarged at 46 mm Two dimensional echocardiography in real time dramatically demonstrated the prolapse of an aortic cusp and a probable vegetation into the left ventricular outflow tract during diastole (Fig 9) The hinge point of the prolapse was the posterior aortic wall The mitral valve leaflets appeared to be normal

On the basis of the above data and the patient s precarious clinical status she was taken to the operating room without prior left heart catheterization The aortic valve leaflets which were covered with multiple vegetations were resected and were replaced with a porcine heterograft

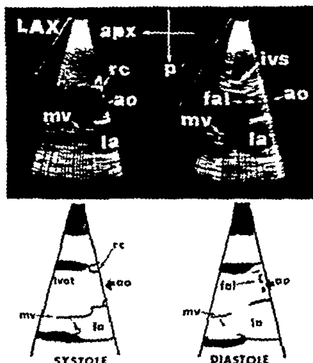


Fig 6 Two-dimensional echocardiogram (LAX) in systole and diastole from Case 2 The aortic leaflets are visualized in the aortic root closely apposed to the aortic wall during systole In diastole a portion of a leaflet is noted to extend below the level of the aortic valve closure line into the left ventricular outflow tract This was more easily appreciated on the dynamic motion display Abbreviations *ao* = aorta *apx* = apex *fal* = flail aortic leaflet *ivs* = interventricular septum *la* = left atrium *LAX* = long axis view *lvot* = left ventricular outflow tract *mv* = mitral valve apparatus *rc* = right aortic cusp



Fig 7 M mode echocardiograms of the aortic root from Case 3 *In the left tracing* of the aortic root and left atrium chaotic systolic flutter of the aortic valve is dramatic and consistent with a flail aortic leaflet *The tracing on the right* taken from a slightly different angle demonstrates aortic leaflet flutter in diastole as well as systole which also suggests a flail aortic leaflet Extra fuzzy echoes in both systole and diastole are consistent with vegetations. Abbreviations *ar* = aortic root *ee* = extra echoes *fl* = flutter *la* = left atrium *?lc* = possible left coronary cusp *nc* = noncoronary cusp *rc* = right coronary cusp

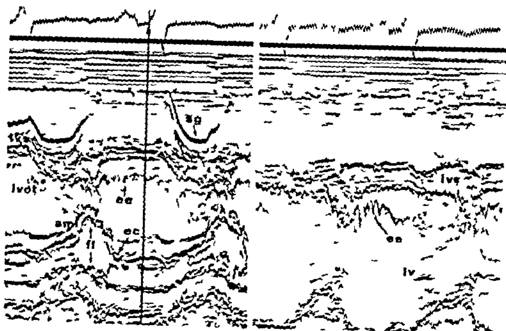


Fig 8 M mode echocardiograms from Case 3 *On the left* the left ventricle is shown at the level of the mitral valve A Swan Ganz catheter is noted in the right ventricle Diastolic mitral valve flutter and early closure of the mitral valve suggesting severe aortic insufficiency are present Extra coarse fluttering echoes are seen during diastole in the left ventricular outflow tract These extra echoes are also seen extending during diastole to a level of the left ventricle below the mitral valve in *the tracing on the right* This combination of findings is consistent with a flail aortic leaflet and or a vegetation prolapsing into the left ventricle and resulting in severe aortic insufficiency Abbreviations *am* = anterior mitral leaflet *ec* = early closure *ee* = extra echoes *fl* = flutter *ivs* = interventricular septum *lv* = left ventricle *lvot* = left ventricular outflow tract *sg* = Swan Ganz catheter

Vegetations on the anterior mitral valve leaflet and interventricular septum were removed A tricuspid annuloplasty was performed

Postoperatively the patient had resolution of her congestive heart failure She was treated with an additional four weeks of antibiotics and was discharged five and a half weeks after surgery in stable condition on digoxin only

Case 4 A previously healthy 16 year old female without known cardiac disease or murmurs was transferred to UCLA for appropriate therapy for presumed infective endocarditis with severe cardiac decompensation She had undergone a therapeutic abortion two weeks prior to admission which was complicated by a purulent sanguinous vaginal discharge

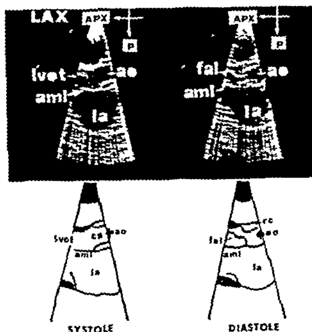


Fig 9 Two dimensional echocardiogram (LAX) from Case 3 The aortic leaflets are visualized in the aortic root in systole During diastole there is abnormal leaflet coaptation and a flail aortic leaflet extends from the posterior aortic wall down into the left ventricular outflow tract A vegetation at the tip of the flail leaflet cannot be ruled out Abbreviations *aml* = anterior mitral leaflet *ao* = aorta *apx* = apex *cs* = aortic cusps *fal* = flail aortic leaflet *la* = left atrium LAX = long axis view *lvot* = left ventricular outflow tract *p* = posterior *rc* = right coronary cusp

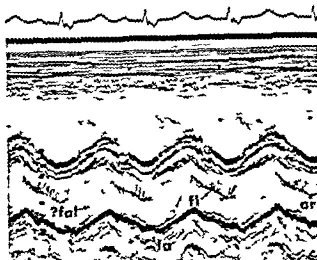


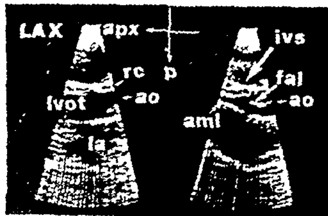
Fig 10 M mode echocardiogram of aortic root from Case 4 High frequency flutter of the aortic valve closure line is noted in diastole suggesting a flail aortic leaflet The posterior noncoronary cusp echo in early systole is shown in the wide-open position but is then noted to drift across the normal systolic aortic opening This may represent the flail leaflet Abbreviations *ar* = aortic root *?fal* = possible flail aortic leaflet *fl* = flutter *la* = left atrium

On initial examination at UCLA she was pale tachypneic and tachycardic with cool mottled skin over the extremities Her blood pressure was 70/30 mm A hyperdynamic left ventricular impulse was palpable in the fifth intercostal space at the midclavicular line A systolic thrill was present at the left lower sternal border The first heart sound was normal with a diminished single second sound A Grade 4/6 systolic murmur was loudest at the left lower sternal border but radiated across the precordium It was characterized as holosystolic versus crescendo decrescendo by various observers A Grade 1 2/6 early decrescendo diastolic murmur was appreciated for the first time There were no gallops The chest examination revealed bibasilar rales There was no peripheral edema Punctate hemorrhages were present on the inner aspect of the left lip A soft suprapubic mass was palpated suggesting an 8 to 10 week size uterus

On M mode echocardiography high frequency diastolic fluttering of the aortic cusp echoes was noted suggesting a flail aortic valve leaflet (Fig 10) The posterior aortic valve cusp was noted to move abnormally across the normal aortic valve opening Mitral valve closure was not premature The left atrium was mildly dilated (40 mm) and the left ventricular diastolic dimension was 50 mm with normal septal and posterior wall motion On the 2 D echocardiogram a portion of the aortic valve extended into the left ventricular outflow tract during diastole and was visualized on both the LAX and SAX views (Figs 11 and 12) Distinct vegetations were not seen on M mode or 2 D echocardiography

The patient was treated for presumed bacterial endocarditis with intravenous antibiotics She underwent emergency dilatation and curettage 12 hours after admission with removal of 25 to 30 grams of necrotic material and port wine colored fluid Her aortic insufficiency murmur became louder The patient suffered two cardiac arrests and was not able to be resuscitated the second time She died 24 hours after admission to UCLA Medical Center

At necropsy the noncoronary cusp of the aortic valve was torn and ragged (Fig 13) There were no gross vegetations present on any of the aortic



SYSTOLE DIASTOLE

Fig 11 Two-dimensional echocardiogram (LAX) in systole and diastole from Case 4 In systole the aortic valve leaflets are clearly shown to be in the aortic root The closed mitral valve is not clearly visualized During the early diastolic frame shown the mitral valve is widely open and a portion of an aortic leaflet extends well below the aortic leaflet closure line Abbreviations aml = anterior mitral leaflet ao = aorta apx = apex cs = aortic cusps fal = flail aortic leaflet ivs = interventricular septum la = left atrium LAX = long axis view lvot = left ventricular outflow tract p = posterior rc = right cusp

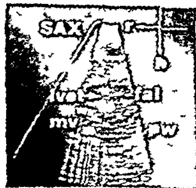


Fig 12 Two-dime[nsional] ... (SAX) from Case 4 A portion of aorti[c] ... [extend]ing into the left ventricular outflow tra[ct] ... aml fluttering of these echoes ... not co... ph[otogr]aph Abbreviations fal = flail ... left [v]entri[cu]lar outflow tract m... pw = posterior wall SAX ...

cusps There was a 1 2 by 0 6 cm perforation of the interventricular septum inferior to this aortic leaflet which extended above the tricuspid valve and communicated with the right atrium The right atrial side of the perforation was surrounded by friable raised dull red vegetations The inferior portion of the defect had a smooth border and was felt to represent a preexisting ventricular septal defect The pulmonic and mitral valves were normal The left ventricle and left atrium were slightly dilated

The history clinical course and pathologic findings are consistent with a bacteremia secondary to pelvic manipulation which resulted in the development of endocarditis at the site of a previous small or closed ventricular septal defect Perforation of the interventricular septum with a left ventricular right atrial shunt developed and the infection eventually involved the (noncoronary) posterior aortic cusp resulting in aortic insufficiency This process may also have damaged the conduction system leading to asystole and cardiac arrest All blood cultures and cultures of the necropsy vegetations grew no organisms Group A alpha hemolytic streptococcus and Group B beta hemolytic streptococci grew from her vaginal cultures and may represent the source of the infection

Results

The results are summarized in Tables I and II

Case 1 The initial M mode echo was very suggestive of right coronary cusp vegetations but thickening of the valve was also possible The dilated left ventricle (LV) with increased wall motion and diastolic mitral valve fluttering were consistent with AI The 2 D echo (Fig 1) was helpful in clearly delineating a very thickened right aortic cusp with normal motion which made the diagnosis of a vegetation much more likely than simply thickening

When the patient clinically decompensated his M mode echo (Fig 2) showed LVOT echoes in diastole suggesting that a portion of an aortic leaflet or a vegetation was prolapsing into the LVOT In addition new early mitral valve closure suggested severe AI The 2 D echo (Fig 3) revealed a flail aortic valve leaflet extending into the LVOT almost touching the anterior mitral valve leaflet This echo was noted to vibrate



Fig. 13. Autopsy specimen from Case 4. The ragged edge *(arrow)* of the flail noncoronary aortic leaflet is outlined against the perforation of the interventricular septum.

Table I. Clinico-pathological information in four patients with flail aortic leaflets

Case	*Sex*	*Age*	*Predisposing factor(s)*	*Organism*	*Anatomic finding at surgery or necropsy*	*Left heart cath*
1	M	31	Dental manipulation	Kingella kingae	Trileaflet thickened aortic valve with one cusp torn, one perforated, and one covered with vegetations	No
2	M	28	None	None	Trileaflet aortic valve with redundant noncoronary cusp and diffuse myxomatous changes	Yes
3	F	3[illegible]	Heroin abuse	Group D Streptococcus (Enterococcus)	Probable trileaflet aortic valve with multiple vegetations. Vegetations on anterior mitral valve leaflet and on interventricular septum	No
4	F	16	Ventricular septal defect, therapeutic abortion	Not determined	Trileaflet aortic valve with torn posterior cusp, defect of interventricular septum connecting left ventricle and right atrium at site of previous VSD; right atrial opening was surrounded by vegetations	No

Abbreviations: F = female; M = male.
* = at necropsy.

vigorously. This motion could not be captured on the Polaroid stop-frame pictures. The hinge point for the motion of the LVOT echo was at the junction of the leaflet with the aortic root, rather than on the body of the leaflet itself as would be expected with a vegetation alone. These findings elucidated the cause of sudden cardiac decompensation in a patient with known AI secondary to vegetations and obviated the need for a left heart catheterization in a significantly decompensated patient prior to surgery. At surgery, a torn cusp was noted in addition to a thickened right cusp

Table II M mode echocardiographic findings

Case	LVDD (mm)	LVVO	Early MV closure	Diastolic flutter MV	Diastolic flutter AV	LVOT echoes	Systolic flutter AV	Vegetation
1 pre	67	±a	–	+	–	–	None	S D
post	70	+	+	+	–	+	None	S D
2	70	±a	+	+	+	–	Fine	–
3	61	±b	+	+	+	+	Chaotic	S D
4	50	–	–	–	+	–	None	–

Abbreviations and symbols AV = aortic valve D = present in diastole LVDD = left ventricular diastolic dimension LVOT = left ventricular outflow tract LVVO = left ventricular volume overload MV = mitral valve post = after clinical decompensation pre = before clinical decompensation S = present in systole + = present – = absent ± = increased left ventricular dimension with (a) increased septal motion and normal LV posterior wall motion or (b) increased posterior wall motion and normal septal wall motion

densely covered with nonmobile vegetations

Case 2 The M mode echocardiogram revealed a dilated left ventricle with increased septal motion consistent with left ventricular volume overload (LVVO) and a dilated left atrium Severe AI was suggested by the combination of a fluttering mitral valve in diastole and early mitral valve closure (Fig 5) Rapid high frequency oscillations of the aortic valve in diastole were prominent and suggested a flail leaflet (Fig 5) On 2 D echo (Fig 6) a portion of the aortic valve was observed to prolapse into the LVOT, confirming the diagnosis suggested on M mode echocardiography Still frame Polaroid pictures could not capture this motion well There was no suggestion of vegetations on either study At surgery a redundant noncoronary cusp which prolapsed into the LVOT was noted There were no vegetations

Case 3 The M mode echocardiogram (Fig 7) revealed striking fluttering of the aortic valve leaflets in both diastole and systole chaotic and coarse in some views suggesting a flail leaflet (either the left or noncoronary cusp) The views of the left ventricle both at and below the mitral valve demonstrated coarse diastolic extra echoes in the LVOT (Fig 8) Either a flail leaflet and/or a vegetation on the ventricular surface of the aortic valve could produce the above picture Two-dimensional echocardiography (Fig 9) dramatically demonstrated that in early diastole the posterior cusp seen on the long axis view abruptly moved (within one frame) into the LVOT with a whip like motion The pivot point of this whip like motion was clearly the aortic wall rather than the aortic leaflet itself In addition the two leaflets seen on the LAX view did not coapt in diastole These findings were diagnostic of a flail leaflet Therefore the etiology of this patient s clinical compromise was determined and surgery was performed without a left heart catheterization A vegetation at the tip of the flailing leaflet could not definitely be ruled out Multiple vegetations were noted at surgery but a comment as to their mobility or exact location was not made

Case 4 Striking M mode findings (Fig 10) in this case were rapid high frequency diastolic vibrations of the aortic valve and abnormal anterior systolic motion of the posterior aortic cusp These two findings were highly suggestive of a flail aortic leaflet There was no evidence of vegetations

On 2 D echo a portion of the aortic valve extended into the LVOT where it vibrated vigorously It was demonstrated on both the LAX and SAX views and was felt to represent a flail aortic leaflet (Figs 11 and 12) This was the only case in which LVOT echoes were noted on the SAX view The etiology of the flail leaflet was not suggested by either the M mode or 2 D study This patient had no vegetations on her flail aortic leaflet at autopsy although vegetations were present on the right atrial side of the interventricular defect

Discussion

The echocardiographic manifestations of a ruptured aortic valve leaflet were initially described by Lee and colleagues In four patients with subsequent anatomical confirmation they noted a band of high frequency echoes (HFE) during early to mid diastole in the aortic root echograms There was no comment on the etiology of the ruptured leaflets

Wray first described the M mode findings of a

flail aortic valve leaflet in bacterial endocarditis Dense disorganized diastolic echoes were noted in the aortic root and in the LVOT in the first patient he described In a series of five patients with aortic valve endocarditis and aortic insufficiency he noted coarse or thin diastolic echoes in the aortic root which move erratically or vibrate and felt these suggested that at least a portion of the aortic valve was flail

The presence of diastolic LVOT echoes secondary to primary aortic valve disease was noted by Gottlieb and associates[1] in two patients with Candida endocarditis However these echoes were felt to represent the bulky fungal vegetations on the aortic valve rather than a flail leaflet

A flail aortic valve leaflet due to myxomatous degeneration in three patients and due to bacterial endocarditis in two was documented pathologically by Whipple and co workers They noted both (1) diastolic LVOT echoes and (2) diastolic fluttering of the aortic valve but added (3) coarse systolic oscillations of the aortic cusp echoes to the described M mode manifestations of flail aortic valve leaflets They interpreted the presence of (2) to be secondary to AI alone but the combination of 1 and 2 to be diagnostic of a flail or prolapsed leaflet A fourth case of a flail aortic valve secondary to myxomatous degeneration with the three echocardiographic features described above was reported by Estevez and associates

Roy and colleagues noted that eight of 32 patients with bacterial endocarditis had LVOT echoes that merged into diastolic aortic valve vibrations In this series LVOT echoes could be seen with vegetations alone or with actual valvular disruption

Chandraratna and co workers described abnormal LVOT echoes in four patients with severe AI three had bacterial endocarditis and one had myxomatous degeneration of the aortic valve (floppy aortic valve) High frequency diastolic fluttering of the aortic valve was noted in the patient with myxomatous degeneration and was similarly seen in another patient with a floppy aortic valve also reported by the same authors

In six other case reports of flail or ruptured aortic valves in patients with definite or presumptive IE the echo findings consisted of various combinations of the diagnostic criteria summarized above

Kleiner and associates[6] described two patients with IE and surgically confirmed flail aortic leaflets in whom dense aortic root echoes were noted in systole but not in diastole with associated diastolic LVOT echoes The dense systolic echoes presumably represented the fluttering flail aortic leaflet which during diastole was present only in the LVOT and was represented by the echoes seen there These workers concluded that this constellation of findings was pathognomonic of a ruptured aortic cusp

Yoshikawa and colleagues reported a case in which the M mode echo revealed diastolic fuzzy aortic valve echoes with fine fluttering diastolic fluttering LVOT echoes and coarse systolic fluttering of the aortic valve These findings were consistent with a flail aortic valve and/or a vegetation on the aortic valve which was large and/or mobile Ultrasonic cross section views in the long axis demonstrated a 3 cm long vegetation extending from the midpoint of aortic valve coaptation into the LVOT in diastole and continuous with the noncoronary cusp in the aortic root during systole The observation that the hinge point of the lesion appeared to be the edge of the posterior cusp rather than the aortic wall led them to conclude the abnormal echo represented a large mobile vegetation At surgery a 3 cm long cordlike vegetation was attached to the ventricular surface of the noncoronary cusp

Two additional examples of surgically confirmed aortic valve IE have been reported with 2 D echocardiography demonstrating vegetations that protruded into the LVOT [8] In one case a long thin vegetation was visualized moving from aortic root to LVOT in systole and diastole respectively coaptation of the aortic cusps was seen in diastole and the vegetation extended down from the midpoint of coaptation into the LVOT In the second case bulky vegetations were seen on all three cusps on 2 D echo which extended below the plane of aortic valve closure into the LVOT Thus in one case LVOT echoes were due to a mobile vegetation and in the second they were secondary to large bulky vegetations In both cases the hinge point of the abnormal echoes was the aortic cusp rather than the aortic wall and diastolic coaptation of the cusps was visualized This made a flail leaflet less likely

M mode findings in these cases were not detailed

A fourth case in which 2 D echo was helpful in clarifying the M mode findings and in diagnosing both a vegetation extending into the LVOT and an aortic root abscess was recently reported

In three of our four patients with a flail aortic leaflet the diagnosis of severe acute AI was suggested by the combination of diastolic MV flutter and early MV closure seen on the M mode echocardiogram Echocardiographic evidence of aortic valve vegetations was present in the two patients with surgically documented aortic valve vegetations Diastolic flutter of the aortic valve was present in Cases 2 3 and 4 LVOT echoes were present in Cases 1 and 3 and coarse systolic flutter of the aortic valve was present in Case 3 The high frequency diastolic flutter of the aortic valve is the most specific M mode finding of a flail aortic leaflet and was present in three of the four cases The additional coarse chaotic systolic flutter of the aortic valve seen in Case 3 further supported this diagnosis Case 1 however had neither of these findings but had LVOT echoes which could have been due to a flail leaflet and/or a vegetation The 2 D echocardiogram in Case 1 was necessary to distinguish between these two possibilities

On two dimensional echocardiography in each case a portion of the aortic leaflet extended into the LVOT demonstrating a flail leaflet This was best seen on the LAX view but was also captured on the SAX view in Case 4 The distinction between a flail leaflet and a vegetation was made by noting the location of the hinge point of the motion of the abnormal echoes into the LVOT The hinge point in these four cases was the aortic wall in contrast to the edge of the aortic leaflet as had been reported with vegetations In Case 3 it is possible that a vegetation was present at the tip of the leaflet in addition to its being flail Abnormal coaptation of aortic leaflets when detected as in Case 3 is further 2 D evidence for a flail leaflet Unfortunately the above findings are best appreciated in real time and are difficult to convincingly capture in still frame photographs

In summary in three patients a flail aortic leaflet could be diagnosed with M mode echocardiography alone although the 2 D echo provided important confirmation In Case 1 the 2 D echo allowed the distinction of a flail leaflet versus a prolapsing vegetation to be made It should be acknowledged, however that in patients with IE and severe AI the distinction between a flail leaflet and a vegetation often can be a moot point and may not affect the eventual treatment plan

Summary

Four patients with documented flail aortic valve leaflets were studied using M mode and two dimensional echocardiography (2 D echo) Two had aortic valve endocarditis one had endocarditis involving a congenital heart defect and one had a myxomatous aortic valve Mitral valve flutter and early mitral valve closure led to the diagnosis of severe aortic insufficiency in three patients Diastolic aortic valve flutter considered to be specific for a flail aortic leaflet was present in three patients In the fourth patient left ventricular outflow tract (LVOT) echoes were present but did not distinguish between a flail aortic leaflet and an aortic vegetation Two D echo confirmed LVOT echoes in all patients Discrimination between a flail leaflet and a vegetation(s) without leaflet disruption was accomplished by noting the hinge point of the LVOT diastolic echoes which was the aortic wall in patients with a flail leaflet

The combination of these M mode and 2 D echocardiographic findings permitted the diagnosis of a flail aortic leaflet to be made accurately and noninvasively In two patients surgery was performed without prior cardiac catheterization

We express our gratitude to Diane Kennedy and Stephanie Thessomboon for their expert technical assistance

REFERENCES

1 Morganroth J Perloff J Zeldis S and Dunkman, B Acute severe aortic regurgitation Pathophysiology clinical recognition, and management Ann Intern Med 87 223 1977
2 Dillon J C., Feigenbaum H Konecke L L., Davis R. H., and Chang S Echocardiographic manifestations of valvular vegetations Am Heart J 86 698 1973
3 Martinez E C., Burch G E and Giles T D Echocardiographic diagnosis of vegetative aortic bacterial endocarditis, Am J Cardiol 34 845 1974
4 Hirschfeld D S., and Schiller N Localization of aortic valve vegetations by echocardiography Circulation 53 280 1976
5 DeMaria A N King J F., Salel A F., Caudill C C. Miller R R and Mason D T Echography and phonography of acute aortic regurgitation in bacterial endocarditis Ann Intern Med 82 329 1975
6 Botvinick, E H Schiller N B Wickramasekaran R. Klausner S C., and Gertz E Echocardiographic demonstration of early mitral valve closure in severe aortic insufficiency Circulation 51 836 1975

7 Rees R Epstein E, Criley M and Ross R Haemodynamic effects of severe aortic regurgitation Br Heart J 26 412 1964
8 Mann T McLaurin L Grossman W and Craige E Assessing the hemodynamic severity of acute aortic regurgitation due to infective endocarditis N Engl J Med 293 108 1975
9 Lee C C Das G and Weissler A M Characteristic echocardiographic manifestations in ruptured aortic valve leaflet (Abstr) Circulation 50(Suppl III) 144 1974
10 Wray T M Echocardiographic manifestations of flail aortic valve leaflets in bacterial endocarditis Circulation 51 832 1975
11 Wray T M The variable echocardiographic features in aortic valve endocarditis Circulation 52 658 1975
12 Gottlieb S Khuddus S A Balooki H, Dominguez A E and Myerburg R J Echocardiographic diagnosis of aortic valve vegetations in Candida endocarditis Circulation 50 826 1974
13 Feigenbaum H Echocardiography ed 2 Philadelphia 1976 Lea & Febiger p 73
14 Whipple R Morris D Felner J Merrill A and Miller J Echocardiographic manifestation of the flail aortic valve leaflet syndrome (Abstr) Circulation 52(Suppl II) 255 1975
15 Estevez C Dillon J Walker P, Feigenbaum H and Chang S Echocardiographic manifestations of aortic cusp rupture in a myxomatous aortic valve Chest 69 685 1976
16 Giuliani E Roy P Tajik A Gau G Schattenberg T and Frye R Abnormal echo in the left ventricular outflow tract in bacterial endocarditis (Abstr) Circulation 52(Suppl II) 69 1975
17 Roy P Tajik A J Giuliani E R Schattenberg T T Gau G T and Frye R L Spectrum of echocardiographic findings in bacterial endocarditis Circulation 53 474 1976
18 Chandraratna P A N Robinson M J Byrd C and Pitha J V Significance of abnormal echoes in left ventricular outflow tract Br Heart J 39 381 1977
19 Chandraratna P A N Samet P Robinson M J and Byrd C Echocardiography of the floppy aortic valve Circulation 52 959 1975
20 Corrigall D Strunk B L and Popp R L Phonocardiographic and echocardiographic features of ruptured aortic valvular cusp Chest 69 669 1976
21 Gaasch W H and Cleveland R J Echocardiographic examination in aortic regurgitation Chest 70 771 1976
22 Fox S Kotler M N Segal B L and Parry W Echocardiographic diagnosis of acute aortic valve endocarditis and its complications, Arch Intern Med 103 85 1977
23 Rolston W A Hirschfeld D S Emilson B B and Cheitlin M D Echocardiographic appearance of ruptured aortic cusp Am J Med 62 133 1977
24 Srivastava T N and Flowers N C Echocardiographic features of flail aortic valve Chest 73 90 1978
25 Ramirez J Guardiola, J and Flowers N C Echocardiographic diagnosis of ruptured aortic valve leaflet in bacterial endocarditis Circulation 57 634 1978
26 Kleiner J P Brundage B H Ports, T A and Thomas H M Echocardiographic manifestations of flail right and noncoronary aortic valve leaflets, Chest 74 301 1978
27 Yoshikawa J Tanaka K Owaki T, and Kato H Cord like aortic valve vegetation in bacterial endocarditis Demonstration by cardiac ultrasonography Report of a case Circulation 53 911 1976
28 Gilbert B W Haney R S Crawford F McClellan J Gallis, H A Johnson M L and Kisslo J A Two dimensional echocardiographic assessment of vegetative endocarditis Circulation 53 346 1977
29 Mardelli T J, Ogawa S Hubbard R E Dreifus L S and Meixell L L Cross-sectional echocardiographic detection of aortic ring abscess in bacterial endocarditis Chest 74 576 1978

Relationship of plasma anti-heparin activity and platelet survival time in coronary disease*

Peter Steele M D
Joseph Rainwater M D **
Denver Colo

Platelets probably contribute to the development of atherosclerosis and its complications Platelet survival time is shortened in patients with atherosclerotic coronary disease [1,2] The storage organelles of platelets contain proteins with heparin neutralizing activity which are released into plasma both in vivo and in vitro in response to platelet aggregating agents [3-7] Increased heparin neutralizing activity has been observed in patients with coronary disease [8,9] A number of drugs with effects on laboratory tests of platelet reactivity have been identified and one of these drugs sulfinpyrazone has been shown to decrease sudden cardiac deaths in survivors of myocardial infarction [10]

In the present study platelet survival time and plasma heparin neutralizing activity were measured in men with coronary disease and the effects of several platelet suppressant drugs on these two tests of platelet reactivity were defined

Patients

Studies were undertaken in 75 men with coronary artery disease All men had undergone coronary arteriography for evaluation of coronary disease Thirty three men had clinical and electrocardiographic evidence for past transmural infarction and 62 men were having angina at the time of study All men had been in a stable clinical condition for at least three months prior to study

Methods

Platelet survival time was measured by labelling the platelets from 300 to 400 ml of the patient s blood with [5]Chromium (100 to 150 microcuries) [11] A single exponent was fitted to seven days of platelet count rate data to obtain the half time This was performed with a computer using least square analysis In 26 normal men platelet survival half time averaged 3 7 ± 0 03 (± SEM) days The range of platelet survival half time was 3 3 to 4 2 days

Plasma heparin neutralizing activity was measured as the patient s heparin thrombin clotting time (platelet poor plasma) divided by the clotting time of normal substrate The result was expressed as a ratio with an average value for [9]5 normal men of 1 10 ± 0 01 and a normal range of 0 96 ± 1 24 (± 2 SD) Abnormally increased levels of plasma heparin neutralizing activity would be expressed as a ratio less than 0 96

Heparin neutralizing activity and platelet survival time were performed simultaneously over a week s time Following control measurements sulfinpyrazone (800 mg orally per day) indomethacin (100 mg orally per day) or aspirin (1 200 mg orally per day) alone and in combination with dipyridamole (100 mg orally per day) were administered and studies were repeated in two to three months In this study patients were not randomly assigned to the treatment groups

From the Divisio f Card logy Departm nt of Med cine Den er Veter ns Administr tion H spital Uni rsity of Col ado Medi l Cente Denver Colorad

Supported by resear h fund f th V ter n Administ ation

Recei ed f r publicat n F b 19 1979

Accepted for publicati M 1 1979

Reprint requests Peter Steel M D V er n Administr tion Medical Center 1055 Clermo t Den C O 80 20

*Presented at the Annual Meet g of th Western Soc ety fo Cl nical Resear h, C rmel, Cal fornia n Febru ry 19 8

**Dr Rainwater is a Research Ass iat f the V ter ns Adm nistr tion

0002 8703/80/040438 + 0 $00 /0/0 © 1980 The C V Mosby Co

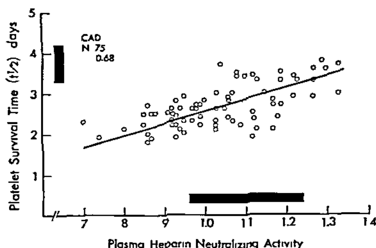


Fig 1 Relationship between platelet survival time and plasma heparin neutralizing activity in men with coronary artery disease *(CAD)* *The solid bars* represent the normal ranges

A second study was undertaken in 12 of these men to define the time course of alteration of heparin neutralizing activity Plasma heparin neutralizing activity was determined each day for eight days after initiating treatment with sulfinpyrazone and after placebo (crossover blinded design)

Statistical analysis was performed using Student s t test All patients understood the purpose and the risk of the study and agreed to participate

Results

Platelet survival time was shortened (< 3 3 days) in 60 men (80%) and averaged 2 6 ± 0 06 days (t 1/2 ± SEM P < 0 001 vs normal) Heparin neutralizing activity was increased (ratio decreased) in 26 men (35%) (ratio patient to substrate < 0 96) and averaged 1 04 ± 0 02 (average ratio ± SEM P < 0 001 vs normal) These two measurements of platelet reactivity appeared to have a relationship with each other (correlation coefficient r = 0 68) (Fig 1) Of the 15 men with normal platelet survival time all had normal heparin neutralizing activity Of the 60 men with shortened platelet survival 26 had abnormal heparin neutralizing activity and this test was normal in the other 34 men Thus in men with coronary disease these two tests of platelet reactivity appear to relate to each other but platelet survival time is more sensitive for the presence of coronary artery disease than is plasma heparin neutralizing activity Of the 33 men with a history of transmural infarction 26 (79%) had shortened platelet survival and 13 (39%) had increased heparin neutralizing activity These frequencies are not different from the frequencies for the group of men without a history of infarction or for the whole group of men with coronary disease

Twenty men with shortened platelet survival received sulfinpyrazone and platelet survival was increased by at least 0 02 days in 14 (70%) (2 5 ± 0 07 to 2 8 ± 0 09 days P < 0 01) Heparin neutralizing activity was decreased by sulfinpyrazone (ratio increased) (1 02 ± 0 03 to 1 19 ± 0 01 P < 0 001) and 18 (90%) had an increase in this ratio by at least 0 03 All three of these men with abnormal control values for heparin neutralizing activity had an alteration with sulfinpyrazone

Indomethacin also increased platelet survival time (2 4 ± 0 08 to 2 7 ± 0 08 days N = 16 P < 0 01) and 11 (69%) had an increase Heparin neutralizing activity was altered by indomethacin (0 98 ± 0 02 to 1 15 ± 0 02 P < 0 001) and 14 (88%) had a decrease in activity All of these 16 men had shortened control platelet survival and three had abnormal control values for heparin neutralizing activity

Twenty four men received aspirin 1200 mg orally per day for two months and then dipyridamole 100 mg orally per day with aspirin for an additional two months with studies repeated Aspirin had a small, but significant effect on platelet survival time (2 4 ± 0 06 to 2 6 ± 0 07 days P < 0 05) and 10 men (42%) had an increase

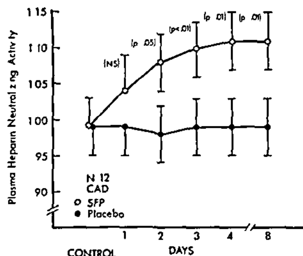


Fig 2 Alteration of plasma heparin neutralizing activity by sulfinpyrazone *(SFP)* in men with coronary artery disease *(CAD)* *The bars represent the standard error*

in platelet survival Aspirin had a more marked effect on heparin neutralizing activity (0 99 ± 0 03 to 1 07 ± 0 02 $P < 0.01$) with 17 men (71%) having an alteration With dipyrida mole and aspirin a further increase in platelet survival time (3 0 ± 0 09 days $P < 0.001$) and a further decrease in heparin neutralizing activity (1 16 ± 0 02 $P < 0.001$) was observed All of these men had shortened control platelet survival and five had increased control values for heparin neutralizing activity

In the platelet suppressant drug studies all men who had an increase in platelet survival also had a decrease of plasma heparin neutralizing activity Measurement of heparin neutralizing activity was more sensitive in respect to demon stration of a drug effect In addition the altera tion of both tests by aspirin was less marked than the alteration by the other drugs

Using a blinded cross over design sulfinpyra zone and placebo were administered to 12 men with coronary disease and shortened platelet survival time and daily measurement of plasma heparin neutralizing activity was undertaken There was a stepwise increase in the ratio (de crease in activity) occurring by the second day with maximal values reached by the fourth day in all men (Fig 2) With placebo heparin neutraliz ing activity was not altered by 0 03 in any patient Thus sulfinpyrazone appears to act promptly to decrease heparin neutralizing activity in men with coronary artery disease

Discussion

The present study confirms previous studies suggesting that platelet survival time is shortened in most patients with atherosclerotic coronary disease[1] Platelet survival time and plasma heparin neutralizing activity appear to be related to each other although this heparin neutralizing activity was within the normal range for most patients with coronary artery disease O Brien and associates[9] observed substantially increased heparin neutralizing activity in patients within several days of an acute myocardial infarction Heparin neutralizing activity decreased towards normal in these patients during convalescence (three months) Dana and associates[9] found increased heparin neutralizing activity in several groups of patients with coronary disease includ ing patients in a stable clinical situation during acute myocardial infarction or during unstable angina Our patients were all in a stable clinical state and there were no differences in heparin neutralizing activity between men with and with out a history of infarction

The relationship between plasma heparin neu tralizing activity and platelet survival time su gests that this neutralizing activity reflects plate let reactivity Platelets contain and release a low molecular weight protein (or proteins) platelet factor four which has heparin neutralizing activ ity It is probably too simplistic to suggest that plasma heparin neutralizing activity measures platelet heparin neutralizing activity since both erythrocytes and leukocytes have heparin neu tralizing activity[12 13] without having the platelet factor four protein[13]

Measurement of plasma heparin neutralizing activity does appear to be a sensitive indicator of platelet suppressant drug effect With this test sulfinpyrazone indomethacin and dipyridamole in combination with aspirin were observed to have a greater effect on plasma heparin neutral izing activity than on platelet survival time Aspirin was shown to have an effect on both platelet survival time and heparin neutralizin activity but this effect was less marked than with the other drugs These data suggest that indo methacin is a platelet suppressant agent which is not surprising in that it shares pharmacologic actions with sulfinpyrazone In addition sulfin pyrazone appears to act quickly as supported by the decrease in plasma heparin neutralizing activ

ity observed as soon as 48 hours after initiating treatment

Although platelet suppressant therapy has been suggested for the prevention of thrombosis it is unclear which drugs and which clinical situations might benefit from their use[1] Platelet suppressant drugs have been shown to decrease thromboembolism in patients with prosthetic cardiac valves external silastic arteriovenous shunts[1] recurrent venous thrombosis and may be effective in preventing venous thrombosis after major surgery[6] and in preventing stroke and death in patients with atherosclerotic cardiovascular and cerebrovascular disease[1] The effectiveness of these drugs in decreasing thrombosis and in altering plasma heparin neutralizing activity would suggest that these tests are of value in thrombotic diseases and that plasma heparin neutralizing activity may be measuring platelet anti heparin activity Radioimmunoassay has been developed which appears to measure platelet factor four and it will be necessary to correlate this measurement with heparin neutralizing activity and with platelet survival in patients with thrombosis

Summary

Platelet endothelial interaction probably plays a role in the development of atherosclerotic vascular disease and its complications Platelet survival time has been found to be shortened and plasma anti heparin activity has been shown to be increased in patients with coronary atherosclerosis Platelet survival (autologous labelling with Chromium) and plasma anti heparin activity (heparin thrombin clotting time of platelet poor plasma) were measured in 75 men with coronary artery disease Platelet survival was shortened (< 3 3 days) in 60 men (80%) and averaged 2 6 ± 0 06 days (AVE t 1/2 ± SEM normal t 1/2 3 7 ± 0 03 days N = 28 P < 0 001) Anti heparin activity was abnormal (< 0 96) in 26 men (35%) and averaged 1 04 ± 0 02 (ratio patient to blank seconds/seconds normal ratio 1 10 ± 0 01 N = 25 P < 0 01) Platelet survival time correlated with anti heparin activity (r = 0 68) Sulfinpyrazone (800 mg daily) and indomethacin (100 mg per day) increased platelet survival and decreased heparin neutralizing activity Dipyridamole (100 mg orally per day) in combination with aspirin (1 200 mg per day) increased platelet survival and decreased anti heparin activity but aspirin alone had a comparatively weak effect on these tests Results suggest that plasma heparin neutralizing activity correlates with platelet survival time in men with coronary artery disease Sulfinpyrazone indomethacin and dipyridamole in combination with aspirin alter platelet survival and heparin neutralizing activity but aspirin alone has a comparatively weaker effect

The authors acknowledge the expert technical assistance of Mr Michael Adams, Mrs Carla Gilbert Jan Lacher Carol Vandello and Margie Anderson

REFERENCES

1 Steele P Battock D, and Genton E Effects of clofibrate and sulfinpyrazone on platelet survival time in coronary artery disease Circulation 52 473 1975
2 Ritchie J L, and Harker L A Platelet and fibrinogen survival in coronary atherosclerosis Response to medical and surgical therapy Am J Cardiol 39 595 1977
3 Niewiarowski S, and Thomas D P Platelet factor 4 and adenosine diphosphate release during human platelet aggregation Nature (London) 222 1269 1969
4 Harada K, and Zucker M B Simultaneous development of platelet factor 4 activity and release of C serotonin Thromb Diath Haemorrh 25 41 1971
5 Nath N Niewiarowski S and Joist J H Platelet factor 4 antiheparin protein releasable from platelets. Purification and properties J Lab Clin Med 82 754 1973
6 Walsh P N, and Gagnatelli G Platelet antiheparin activity storage site and release mechanism Blood 44 157 1974
7 Nath N Lowery C T, and Niewiarowski, S Antigenic and antiheparin properties of human platelet factor 4 (PF4) Blood 45 53 1975
8 O'Brien J R Etherington M D Jamison S, Crawford D Sussex J and Lincoln S V Heparin neutralizing activity test in the diagnosis of acute myocardial infarction J Clin Pathol 28 975 1975
9 Dana B Ellman L Carvalho A Daggett W and Hutter A M Jr Plasma heparin neutralizing activity in coronary artery disease Am J Cardiol 38 9 1976
10 The anturane reinfarction trial research group Sulfinpyrazone in the prevention of cardiac death after myocardial infarction The anturane reinfarction trial N Engl J Med 298 289 1978
11 Aster R H Effect of anticoagulant and ABO incompatibility on recovery of transfused human platelets Blood 26 73 1965
12 Poplawski, A and Niewiarowski S Method of determining antiheparin activity of platelets and erythrocytes Thromb Diath Haemorrh 13 149 1965
13 Staba H J Roberts H R and Herion J C Antiheparin activity of lysosomal cationic proteins from polymorphonuclear leukocytes Blood 31 369 1968
14 Hawiger J Collins R D and Horn R G Precipitation of soluble fibrin monomer complexes by lysosomal fraction of polymorphonuclear leukocytes Proc Soc Exp Biol Med 131 349 1969
15 Niewiarowski, S Lowery C T Hawiger J Millman M and Timmons, S Immunoassay of human platelet

factor 4 (PF4 antiheparin factor) by radial immunodiffusion J Clin Lab Med 87 720 1976
16 Genton E Gent M, Hirsh J and Harker L A Platelet inhibiting drugs in the prevention of clinical thrombotic disease N Engl J Med 293 1174 1236 1296 1975
17 Sullivan J M Harken D E and Gorlin R Pharmacologic control of thromboembolic complications of cardiac valve replacement N Engl J Med 284 1391 1971
18 Kaegi A Pineo G F Shimizu A Trivedi H Hirsh J, and Gent M Arteriovenous-shunt thrombosis prevention by sulfinpyrazone N Engl J Med 290 304 1974
19 Steele P Ellis J H Jr and Genton E Effects of platelet suppressant anticoagulant and fibrinolytic therapy in patients with recurrent venous thrombosis Am J Med 64 441 1978
20 Harris W H Salzman E W Athanasoulis C A, Waltman A C and DeSanctis R W Aspirin prophylaxis of venous thromboembolism after total hip replacement N Engl J Med 297 1246 19 7
21 Medical Research Council (Report of the Steering Committee) Effect of aspirin on postoperative venous thrombosis Lancet 2 441 1972
22 Blakely J A and Gent M Platelets drugs and longevity in a geriatric population in J Hirsh J F Cade A S Gallus et al editors Platelets drugs and thrombosis Basel 19 5 S Karger P 284
23 Barnett H J M Canadian cooperative platelet inhibiting drug trial in threatened stroke Stroke 9 110 19 8
24 Gjesdahl K Platelet factor 4 (PF4)—an electroimmunoassay for PF4 in human plasma Scand J Haematol 13 232 1974

The effect of acebutolol on cardiac arrhythmias in patients with chronic coronary artery disease

Dieter Burckhardt, M.D.
Ernst A. Raeder, M.D.
With the technical assistance of Elisabeth Blum
Basel, Switzerland

The use of beta adrenergic blocking agents in the treatment of cardiac arrhythmias is gaining increasing importance, particularly in patients with concomitant coronary artery disease or hypertension. In view of the well known extracardiac side effects, efforts are directed toward development of agents with specific action on cardiac beta receptors. Acebutolol has been shown to be a relatively cardioselective drug with weak intrinsic sympathomimetic activity. While its short term effect in decreasing the incidence of ventricular extrasystoles is well documented, it is not known whether acebutolol is also capable of lessening the severity of ventricular arrhythmias and the frequency of exercise induced arrhythmias. This double blind cross-over clinical trial was therefore designed to quantitate the effects of acebutolol on the grade of ventricular arrhythmias and on the incidence of stress induced arrhythmias.

Materials and methods

Subjects. We studied 15 patients (12 men and three women with a mean age of 57 ± 10.6 years) who had chronic coronary artery disease documented by old myocardial infarction or abnormal coronary arteriograms (≥ 75% luminal narrowing of at least one of the main vessels) or patients who had undergone an aortocoronary bypass operation. Patients with conduction disturbances, congestive heart failure, chronic obstructive lung disease, hypotension, or severe metabolic disease were excluded from the study. Except for digitalis and nitroglycerin, no cardioactive drugs were permitted. Patients entered the study on the basis of a preliminary 4 hour Holter ECG in which at least one episode with a minimum of 12 VPBs/minute or arrhythmias of a higher degree were required.

Drug testing. The investigation was carried out in two periods of four weeks each. In the first period, patients were randomly started on an oral dose of either placebo or acebutolol, 200 mg twice daily. At the end of weeks 2, 4, 6, and 8, a 4 hour long term ECG (LECG) was recorded. At the end of weeks 4 and 8 patients were in addition exercised on a bicycle ergometer with 80 watts. The ECG was written continually throughout the exercise test (6 minutes) as well as after exercise (5 minutes) to permit evaluation of arrhythmias. For the interpretation of exercise tests we noted the highest heart rate reached and the number of ventricular premature beats (VPBs). LECGs were classified according to the highest grade of arrhythmias reached using a modified classification of Lown:

0 = no VPBs
1 = < 12 VPBs/minute
2 = ≥ 12 VPBs/minute
3 = multifocal VPBs
4 = 2 to 4 VPBs in a row and/or R on T phenomenon
5 = ventricular tachycardia (≥ 5 VPBs in a row)

The worst of the two placebo and acebutolol tracings were compared.

From the Division of Cardiology, Department of Internal Medicine, University Hospital, Basel, Switzerland.

Received for publication Feb. 22, 1979.
Accepted for publication March 20, 1979.

Reprint requests: Dieter Burckhardt, M.D., Division of Cardiology, University Hospital, CH-4031 Basel, Switzerland.

0002-8703/80/040443 + 03$00.30/0 © 1980 The C. V. Mosby Co.

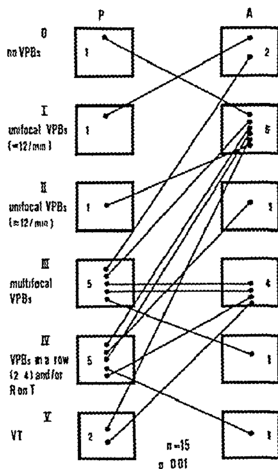


Fig 1 Severity of ventricular arrhythmias during Holter monitoring P = placebo A = acebutolol Note that quantification of VPBs is based on a one minute write out of the worst episode recorded

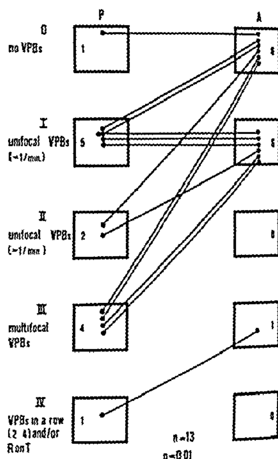


Fig 2 Severity of exercise induced ventricular arrhythmias during administration of placebo (P) and acebutolol (A)

For statistical analysis we used the Wilcoxon test for paired samples Data are reported as mean ± standard error of the mean ($\bar{x}$ ± SEM)

Results

The results of the Holter recordings are shown in Fig 1 Comparison of the grade of arrhythmias in the placebo and acebutolol periods disclosed a favorable effect of acebutolol in 10 patients a worsening in three and no effect in two patients Classification of the most severe arrhythmia recorded nevertheless revealed a decrease from an average grade of 3 2 ± 0 35 (placebo) to 1 9 ± 0 38 (acebutolol) (p = 0 01) While on placebo 20% of our patients were in Class 0 to II and 80% were in Class III to V whereas during the acebutolol period the corresponding proportions were 60% and 40

During and after exercise acebutolol decreased the incidence of ventricular arrhythmias from 18 15 ± 7 7 VPBs in the placebo period to 3 46 ± 1 7 VPBs in the acebutolol period (−81% p < 0 0025) The maximum heart rate reached during exercise was slower in the acebutolol group (96 2 ± 4 7) than in the placebo group (121 8 ± 7 1) (p < 0 0005) Grading of arrhythmias induced by exercise revealed a significant improvement from a mean of 1 92 ± 0 33 (placebo) to 0 69 ± 0 24 (acebutolol) (p < 0 01 Fig 2)

Discussion

There is general agreement in the literature that in patients with coronary artery disease ventricular arrhythmias may presage sudden death Although it is not quite as clear to what extent treatment of these arrhythmias influences mortality from sudden death it is a commonly used policy to treat certain ventricular arrhythmias in the hope to improve prognosis Despite intense efforts an ideal antiarrhythmic drug which reliably suppresses ventricular arrhythmias and which has no serious side effects has not yet been found Beta blocking agent

would appear to be particularly well suited for patients with coronary artery disease since they are part of the standard medical regimen in the treatment of angina pectoris Their antiarrhythmic action may be a direct consequence of adrenergic blockade and/or a membrane stabilizing property or it may be mediated by its favorable effect on myocardial ischemia Clinical efficacy of single and multiple doses of acebutolol in lowering the incidence of ventricular arrhythmias has been shown previously [7] The present study disclosed ventricular arrhythmias of a significantly lower grade after oral administration of acebutolol However despite this significant difference a slight worsening was seen in three patients From our study in which acebutolol was given in a dosage of 200 mg twice daily it would appear that lower doses of this drug than reported by Gradman and colleagues (300 mg three times daily) achieve satisfactory results

One can conclude that acebutolol is a well tolerated drug which favorably influences incidence and severity of ventricular arrhythmias even in moderate oral doses in patients with chronic coronary artery disease

Summary

The effect of the beta blocking drug acebutolol on the severity of cardiac arrhythmias and the incidence of exercise induced arrhythmias was studied in 15 patients with chronic coronary artery disease using ambulatory Holter monitoring and bicycle ergometry We found a significantly lower grading of arrhythmias both on long term ECGs and during and after exercise Furthermore there was a significant decrease in the incidence of VPBs during and after exercise (18 15 ± 7 7 on placebo vs 3 46 ± 1 7 on acebutolol) It is concluded that acebutolol favorably influences the incidence and severity of ventricular arrhythmias in patients with chronic coronary artery disease

REFERENCES

1. Basil B Jordan R Loveless A A and Maxwell, D R Pharmacological properties of M + B 1/803 a a cardioselective beta adrenoceptor blocking agent J Pharmacol. Fr 2 19? 1971
2. Gradman A. H., Winkle R A., Fitzgerald J W., Meffin P J Stoner J III Bell, P A and Harrison D C Suppression of premature ventricular contraction by acebutolol Circulation **55** 785 1977
3. Lown B and Wolf M Approaches to sudden death from coronary heart disease Circulation **44** 130 1971
4. Kotler M N Tabatznik B Mower M M and Tominaga S Prognostic significance of ventricular ectopic beats with respect to sudden death in the late postinfarction period, Circulation **47** 959 1973
5. Wilhelmsson C., Wilhelmsen L., Vedin J A., Tibblin G and Werko L Reduction of sudden deaths after myocardial infarction by treatment with alprenolol Lancet **2** 1157 1974
6. A Multicentre International Study Improvement in prognosis of myocardial infarction by long term beta adrenoreceptor blockade using practolol, Br Med J **3** 735 1975
7. Aronow W S Turbow M., Lurie M Whittaker K., and van Camp St. Treatment of premature ventricular complexes with acebutolol, Am J Cardiol **43** 106 1979

Clinical and morphological features of human hypertensive-diabetic cardiomyopathy

Stephen M Factor M D
Takashi Minase M D
Edmund H Sonnenblick M D
Bronx N Y

Chronic congestive heart failure is a common and serious complication of diabetes mellitus in man[1] Although usually ascribed to the effects of obstructive extramural coronary artery disease recent data suggest that myocardial dysfunction may be associated with diabetes mellitus in the absence of extensive coronary artery atherosclerosis These observations have given rise to the concept of diabetic cardiomyopathy The pathogenesis of this cardiomyopathy is unknown but proposed mechanisms include small vessel (intramural) coronary artery disease interstitial myocardial accumulation of glycoprotein and collagen and metabolic alterations of the diabetic myocardium To date most morphological studies of the diabetic heart in failure have not revealed sufficient abnormalities of the myofiber or interstitium to reasonably account for marked diminution of ventricular function

Although there is an increased prevalence of hypertension among diabetic patients the role of high blood pressure in the genesis of clinical diabetic myocardial dysfunction has not been clear Most published studies of diabetic cardiomyopathy have specifically excluded patients with diastolic hypertension from analysis However hypertension may play an important role in the development of cardiomyopathy in diabetics for it is felt to have adverse cumulative effects on the cardiovascular system in these patients

The purpose of this report is to describe detailed clinical and pathological observations in a consecutive series of nine diabetic patients with severe congestive heart failure who had minimal extramural coronary artery disease Of significance although elevated blood pressure was not a criterion for inclusion in this study all diabetic patients with cardiomyopathy examined in our institution during a two year period were found to have clinically documented hypertension These patients were compared to appropriate control groups in an attempt to delineate the specific effects of diabetes mellitus and concurrent hypertension on the heart We believe that the evidence presented below supports the hypothesis that in at least some patients diabetic cardiomyopathy results from the combination of diabetes mellitus and high blood pressure acting in tandem

Materials and methods

The autopsy records of the Bronx Municipal Hospital Center and the Hospital of the Albert Einstein College of Medicine were reviewed for the years 1976 and 1977 All adult patients with diabetes mellitus for more than 5 years duration and with a history of chronic congestive heart failure were selected for further study Only patients with diabetes mellitus requiring oral hypoglycemic agents or insulin therapy were included Patients under 40 years of age or patients with severe extramural coronary artery

From th Departments of P thology and Med in Albert Einstein College of Medicine Bronx, N Y

Supported in part by National I st t es of Health G ants AM ?0541 and HL-204?6

Recei ed for publicat on Aug 6 19 9

Accepted for publication Oct 19 19?9

Reprint requests Stephen M. Facto M D D f P th logy Albert Ein tein Colleg of Medicine 1300 M rr. P k A e B o x N Y 10461

000? 8?03/80/040446 + 13$01.30/0 © 1980 The C V Mosby Co

disease (greater than 50% narrowing of the lumen) were excluded Also eliminated were patients with a history of alcohol abuse hemochromatosis rheumatic or degenerative valvular disease syphilis or systemic vasculitis Nine patients were identified who fulfilled these criteria

The clinical histories and general postmortem findings were carefully reviewed Patients were classified as hypertensive if the systolic pressure was greater than 140 mm Hg and/or the diastolic pressure was greater than 90 mm Hg on more than one determination or if there was a history of documented high blood pressure requiring medical treatment prior to terminal hospitalization Clinically apparent symptoms of ischemic heart disease such as angina pectoris or previous myocardial infarction were noted as were complications of diabetes mellitus such as peripheral vascular disease nephropathy neuropathy or retinopathy The diagnosis of congestive heart failure was based on physical examination and/or historical evidence of recurrent pulmonary edema dyspnea orthopnea and peripheral edema requiring appropriate therapy

The postmortem examinations were supervised by one of us (S M F) in all but one instance The hearts were sectioned either with horizontal slices from apex to base or were opened in standard fashion with cuts parallel to the long axis of the septum Heart weights and ventricular wall thickness at the outflow tract were recorded Multiple random blocks of myocardium (a minimum of six) were removed from all cavities as well as portions of obviously necrotic or fibrotic tissue The coronary arteries were sectioned at 5 mm intervals with histology performed on all rings demonstrating luminal compromise All tissues were fixed in 3 7% formaldehyde and were processed routinely Tissues were stained with hematoxylin eosin Masson s trichrome stain for connective tissue periodic acid Schiff with and without diastase pretreatment and van Gieson s elastica stain

The microscopic analysis was semi quantitative and was based on studies of all histologic sections from each case The sections were measured to determine the amount of tissue per slide in square centimeters The slides were scanned at 10× magnification and the number of vessels approximately 50 to 200 microns in diameter as determined by an eyepiece micrometer were evaluated Vessels with sclerosis and/or perivascular fibrosis were tabulated and a numerical ratio of abnormal vessels per square centimeter of tissue was calculated for each slide and for the entire case Vascular sclerosis was defined as vessels with intimal and medial hyperplasia and/or fibrosis elastic tissue proliferation and the deposition of PAS positive material in the vessel wall Perivascular fibrosis was defined as the presence of perivascular connective tissue which encroached upon and appeared to involve the adjacent myocardium Both of these parameters of intramyocardial small vessel disease have been described previously[30]

Two types of pathological fibrotic myocardial lesions were described and graded Interstitial fibrosis was defined as areas of collagen deposition surrounding small vessels (less than 50 microns in diameter) and encircling individual or groups of myocardial fibers These were graded 1+ if patchy 2+ if they involved less than one third of the sections 3+ if they involved one third to two thirds of the sections and 4+ if they occurred in more than two thirds of the sections Scars were defined as confluent areas of fibrosis more than 500 microns in greatest dimension These were graded as 1+ if seen rarely 2+ if seen with moderate frequency and 3+ if seen frequently in each of the tissue sections examined

Myocytolysis was defined as a process involving groups of necrotic myocardial cells demonstrating loss of cytoplasmic constituents often with preservation of nuclear detail eliciting a mononuclear cellular inflammatory response and usually associated with interstitial hemorrhage Contraction band type of necrosis was also included in this category The lesions were graded as 1+ 2+ or 3+ based on their frequency in each slide and in the entire case similar to the quantitation of focal scars as described above PAS positive material evaluated in diastase treated sections was graded in a like manner

Upon recognition that our original study group consisted of nine patients with hypertension as well as diabetes mellitus (HD) it became necessary to evaluate the separate effects of both diseases on the heart Accordingly we selected three approximately age matched control groups from autopsies performed by the anatomic pathology service of the Bronx Municipal Hospital Center

The diabetic group (D) consisted of five patients who had adult onset diabetes mellitus

Table 1 Hypertensive-diabetic cardiomyopathy Clinical summary

Case no	Age/ sex/race	Duration of DM (years)	DM treatment	Blood pressure	CHF	KW	Other finding	Caus
1	63/M/B	34	Insulin	Shock, Hx ↑ BP	+	+	S/P BK amputation	DM co
2	47/F/B	7	Diabenase	200/90	+	+	S/P BK amputation	CHF
3	42/F/B	10	Insulin	170/100	+	+	S/P BK amputation	DM co
4	58/M/B	7	Insulin	160/96	+	+	S/P BK amputation	CHF
5	70/M/W	20-25	Insulin	160/80	+	−	S/P cholecystectomy	Acute n
6	67/M/W	20	Insulin	Shock, Hx ↑ BP	+	+	GI hemorrhage	GI hem
7	46/M/B	20	Insulin	180/96	+	+	Renal failure	Uremia
8	70 F/W	10	Diabenase	300/190	+	−	Bronchopneumonia	Bronch
9	63/M/W	6	Insulin	Hx ↑ BP	+	+	S/P BK AK amputation	Bronch

Abbreviation DM = diabetes mellitus CHF = congestive heart failure KW = Kimmelstiel Wilson disease

with no clinical or pathological evidence of hypertension The duration of disease the levels of hyperglycemia and the form of treatment were comparable to the HD group The hypertensive group (H) comprised five patients with hypertension as defined above but with no diabetes mellitus The levels of systolic and diastolic blood pressure were comparable to those in the HD patients The normal group (N) was composed of five patients who died of non cardiac disease with no clinical or pathological evidence of diabetes mellitus or hypertension None of the patients in the three control groups had large coronary artery disease involving more than 50% of the luminal diameter The smaller size of the control groups compared to the HD study group was a result of difficulty in identifying normotensive diabetics or of finding either hypertensive or normal patients without significant coronary atherosclerosis in the age range required by this study

Statistical comparison of the four groups was performed by means of the Mann Whitney non parametric test and Student's t test where appropriate A 2p value less than 0.05 was considered statistically significant

Results

Clinical findings (see Table I) The hypertensive-diabetic group (HD) was composed of three women and six men The [illegible] 58.4 years Six of the nine had been d[illegible] more than 10 years (mean for the entire [illegible] years) Two patients were treated with [illegible] while seven were insulin-dependent Six [illegible] were hypertensive on admission to the h[illegible] while three were in shock but had a history of h[illegible] pressure Of interest despite the fact t[illegible] nine patients had no evidence of occlu[illegible] coronary artery disease at autopsy [illegible] peripheral vascular disease necessitat[illegible] extremity amputation Two patients [illegible] clinical diagnosis of an acute myocardi[illegible]tion prior to their terminal hospi[illegible] although postmortem examination re[illegible] evidence of an old infarction Seven pat[illegible] the clinical diagnosis of diabetic glomer[illegible]sis although only one patient had [illegible] azotemia and proteinuria Kimmelsti[illegible] disease (nodular glomerulosclerosis) [illegible]firmed pathologically in these seven pat[illegible] nine HD patients had long standing cl[illegible]dence of congestive heart failure requir[illegible]cal therapy

The diabetic group (D) was compos[illegible] men and three women with a mean a[illegible] years Four patients in this group we[illegible] dependent No patient had a blood [illegible] recording higher than 130/75 mm Hg [illegible] there any evidence of congestive hear[illegible] One patient had Kimmelstiel Wilson [illegible] Although the group is small it may be re[illegible] note the relative infrequency of nodular [illegible]losclerosis in this normotensive series of [illegible] with long standing diabetes mellitus [illegible]tients died as a direct result of their [illegible] mellitus while one died of chronic pyelo[illegible] and two died of malignancy

The hypertensive group (H) was com[illegible] two men and three women with a mea[illegible] 58.2 years None had a history of chroni[illegible]tive heart failure although one patient h[illegible]



Fig. 1. This horizontal section of left and right ventricle from Case No. 6 demonstrates marked biventricular hypertrophy. The left ventricular wall has a diffuse paleness secondary to extensive interstitial connective tissue deposition. The coronary artery *(thick arrow)* is widely patent. Several focal dark areas, which are particularly well seen in the papillary muscle *(thin arrow)*, represent zones of recent myocytolysis.

Table II. Hypertensive diabetic cardiomyopathy: pathology

Case no.	*Heart weight (gms)*	Thickness (cm)		*Scars*	*Interstitial fibrosis*	*PAS (+)*	*Myocytolysis*	*PVF**	*VS*
		LV	*RV*						
1	3 0	1 8	0 5	3+	3+	?+	-+	1 6	1 1
	4 0	1 6	0 3	?+	2+	?+	–	1.2	0.8
3	xi	0	1 0	3+	?+	2+	–	2.3	1.3
4	400	1 6	0 4	2+	4+	2+	1+	3.9	1 4
	4 0	1 6	0 5	3+	4+	3+	1+	5 4	?9
6	6 0	1 9	0.5	3+	4+	3+	3+	4 4	2.3
	4>0	?0	0.5	?+	4+	1+	1+	2 1	0 3
8	600	1 5	0 6	3+	4+	3+	1+	? 0	3 4
9	600	-5	1 0	1+	4+	+	1+	? 1	0.8
Mean	> 4	1.8	0 6	2 4+	3 4+	2.2+	1 1+	3 6	1 ?

Abbreviations: PVF = perivascular fibrosis; VS = vascular sclerosis.
*Mean vessel ... m

failure following a subarachnoid hemorrhage. Blood pressures ranged from 170/110 to 260/110 mm Hg. Four patients died of acute subarachnoid or intracerebral hemorrhage, while one patient succumbed to chronic renal failure secondary to multiple myeloma.

The normal group (N) was composed of fiv... women with a mean age of 51.6 years. There wa... no history of hypertension, diabetes mellitus, no... congestive heart failure. The causes of deat... included extensive burn, septic shock, metastat... carcinoma (two), and massive upper gastrointes...



Fig 2 This view of the sectioned ventricular septum from Case No 5 reveals a large zone of myocytolysis, with a characteristic depressed hemorrhagic and semitranslucent appearance Surrounding this area are several foci of fibrosis

Table III Comparative pathology Hypertensive diabetics versus controls

Group (number)	*Heart weight (gm)*	*Scars (grade)*	*Interstitial fibrosis (grade)*	*Myocytolysis (grade)*	*PVF**	*VS*
Normal (5)	26_ ~ 69	0 4	0 6	0 4	2 0 ± 1 0	1 4 ± 0 6
Diabetic (5)	349 ± 68	0 4	0 4	0	4 0 ~ 0 7	1 3 ± 0 [illegible]
Hypertensive (5)	434 ~ 9	1 4	1 6	0	3 4 ~ 1 4	1 2 ~ 0 6
Hypertensive-diabetic (9)	[illegible]3 ~ 105	2 4	3 1	1 1	3 6 ± 1 6	1 5 ± 1 0
Significance	HD vs H NS D p [illegible] N p [illegible]	HD vs H p < 0 05 D p < 0 01 N p < 0 01	HD vs H p < 0 01 D p < 0 01 N p 0 01	HD vs H p < 0 01 D p < 0 01 N p < 0 01	HD vs H NS D NS N NS	HD vs H [illegible] D [illegible] N [illegible]

Note 1 All figures represent mean with standard deviations calculated for the numerical determinations (Heart weight PVF VS)
Statistical anal [illegible] h num [illegible] d term nat ons was by means of Student s t test that for the graded d [illegible] rminations wa by means of the Mann Whitne [illegible] pa ame [illegible] tes
3 PVF = peri [illegible] ula [illegible]
Mean [illegible] essel [illegible]

tinal hemorrh[illegible] n a pa [illegible] with adenocarcinoma of the end[illegible]metrium

Pathological findings (see Tables II and III)

Macroscopic observations The HD hearts had a characteristic gross [illegible] (Fig 1) There was marked concentr[illegible] [illegible] ricular hypertrophy with an over all heart weight of 529 ± 105 grams (mean ± S D) [illegible] with heart weights of 434 ± 97 grams in the H group 349 ± 68 grams in the D group and [illegible]2 ± 69 grams in the N group The blood pressure range of the HD and H patients was comparable *Two* major changes were noted in the HD hearts in comparison with the three other groups The HD hearts had a firm almost waxy consisten[illegible] resembling the consistency of hearts with diffuse interstitial amyloidosis (amyloid stain were

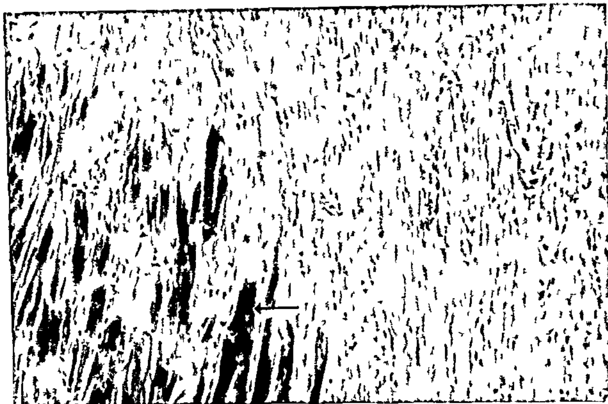


Fig 3 A focal scar from Case No 7 is densely collagenized but the appearance of the tissue is suggestive of a healed myocytolytic zone Supporting this interpretation the residual myocardial fibers in the area are undergoing contraction band necrosis *(arrow)* In other histological sections from the nine cases the evolution of these focal scars could be clearly traced from stages of acute myocytolysis through early collagen deposition *(see Fig 6)* to finally dense fibrosis (Trichrome stain original magnification ×200)

negative in all nine cases) This firmness was probably a result of extensive connective tissue and associated PAS positive glycoprotein deposition in the HD hearts (*vide infra*) The firm waxy quality of the myocardium was not appreciated in any of the three control groups even in the comparably hypertrophied H hearts The other characteristic alteration was the frequency of depressed hemorrhagic semi translucent focal lesions in the HD hearts (Fig 2) These areas were most commonly noted in the subendocardial and midwall myocardium Histology of these zones revealed the presence of active and healing myocytolysis

Small focal areas of gross scarring were commonly observed in the HD hearts rarely in the H hearts and not at all in the other two groups The left ventricular wall thickness was greater than 1.5 cm in all nine HD hearts and in four of five H hearts while it was normal in the other controls Right ventricular wall thickness was greater than 0 5 cm in three of nine HD one of five H and none of five D and N hearts Extramural coronary artery atherosclerosis did not compromise the lumen of any vessel by more than 40% in any of the four groups

Microscopic observations Focal myocardial scars were common in the nine HD hearts (Fig 3 Tables II and III) Transitional zones of scar formation were observed in areas of myocytolysis and it is presumed that the healing of this latter process results in focal scar lesions In all but one HD heart scars were graded as either 2+ or 3+ in frequency whereas in the H hearts they were present to a lesser degree The differences between the two groups were significant at the 0 05 level Similar scarring was noted in just two hearts of the D and N groups and in each of these it was present with only a 1+ frequency

The most striking microscopic feature of the HD hearts was the distribution of dense interstitial connective tissue throughout the myocardium (Fig 4 Tables II and III) The fibrous tissue frequently surrounded individual or groups of

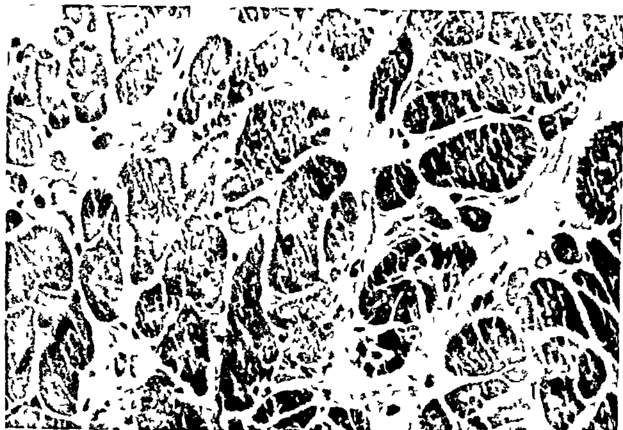


Fig 4 This section of left ventricular myocardium from Case No 6 demonstrates diffuse interstitial fibrosis There is marked variability of myocardial cell size with virtually every cell surrounded by dense collagen This abnormality was a characteristic feature of the hypertensive-diabetic hearts (Hematoxylin-eosin original magnification ×250)

muscle cells completely isolating them There was no obvious relationship between the presence of interstitial connective tissue and abnormalities of vessels in the 50 to 200 micron size range However whether such fibrosis was related to alterations of smaller blood vessels could not be ascertained with the light microscope In all but three HD cases the interstitial fibrosis had a frequency of 4+ in comparison with mild to moderate (1 to 2+) fibrosis in the H group and minimal (0 to 1+) fibrosis in the D and N groups The differences between the HD patients and the three other groups were significant at the 0 01 level

Semiquantitative evaluation of PAS positive diastase resistant material revealed it to be common in the HD hearts and rare in the three other groups It was of interest that the material was invariably localized to areas of interstitial fibrosis or scars (Fig 5) and seemingly was absent in areas of normal myocardium Occasional foci of PAS positivity were observed in fibrotic lesions in the three control groups Similarly intramyocardial vessels in all four groups demonstratin vascular sclerosis or perivascular fibrosis ha PAS positive material in their walls

Foci of myocytolysis were observed in all bu two hearts from the HD patients (Fig 6 Tables I and III) The frequency varied in the group however it was present at a grade of 2+ and 3+ in two cases In contrast myocytolysis was not noted in any of the H or D hearts while grade 1+ was seen in two N controls

Evaluation of intramyocardial vascular changes revealed surprising semiquantitative results Although we fully expected significant alterations in the HD hearts in fact we we e unable to detect statistical differences in any of the four groups (Table III) Both perivascula fibrosis and vascular sclerosis (Fig 7) subjectively appe ared more severe in the HD and H heart However the tabulation of abnormal vessels per square centimeter of tissue examined clearly revealed no statistical differences Since the com parison was numerical rather than an evaluation of the degree of abnormality in each vessel the

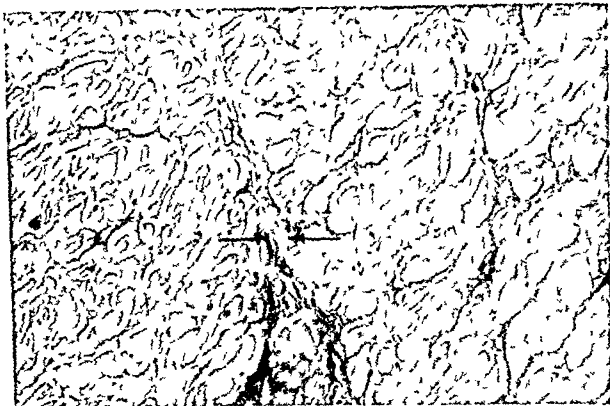


Fig 5 This PAS stained section of left ventricular myocardium reveals PAS positive diastase resistant material predominantly localized to areas of interstitial fibrosis (arrow). Regions of myocardium devoid of pathological connective tissue deposition were equally devoid of PAS positive material. This was a consistent observation in this series of hypertensive diabetic patients. PAS positive material did not diffusely infiltrate the myocardium nor was it observed frequently in the diabetic control group. (PAS stain after diastase pretreatment, original magnification ×200.)

figures tend to understate the differences between groups. In fact, the vascular abnormalities in the HD and H hearts were more severe qualitatively than in either the D or N hearts.

Discussion

The cardiovascular complications of diabetes mellitus comprise a significant proportion of the morbidity and mortality of this disease. Although many of these complications result from the effects of atherosclerosis, recent epidemiologic, clinical, and experimental data suggest that there may be a specific cardiomyopathy causing congestive heart failure in the absence of extramural coronary artery atherosclerosis. This diabetic cardiomyopathy has not been well characterized either clinically or pathologically. In particular, interactions between diabetes mellitus and other diseases, such as hypertension, have not been investigated for their potential causal role in the development of primary myocardial failure. The present report describes the clinical and postmortem pathologic features of nine diabetic patients with congestive cardiomyopathy; the data suggest that hypertension is significantly related to the pathogenesis of severe diabetic heart disease.

Although at least one major study has disputed the increased prevalence of hypertension in the diabetic population, most recent reports have amply documented this association. Christlieb and co-workers at the Joslin Clinic have demonstrated that hypertension in the diabetic is usually a consequence of widespread arteriolar hyalinization, increasing peripheral vascular resistance, and decreased renal free water clearance, producing a high circulating blood volume. This form of hypertension is commonly hyporeninemic and hypoaldosteronemic. Of particular relevance, seven out of the nine hypertensive and diabetic patients in our study had histological evidence of renal disease with

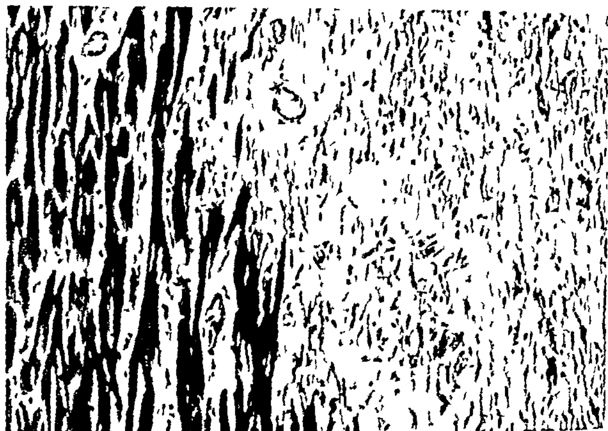


Fig 6 This area of recent myocytolysis from Case No 5 is characterized by many empty spaces representing sites of myocardial cell dropout proliferating fibroblasts chronic inflammatory cells hemorrhage and capillaries. Early collagen deposition is occurring within the zone The residual myocardium is generally well preserved, although the cells are surrounded by interstitial fibrosis (Trichrome stain original magnification ×?00)

typical diabetic lesions of nodular glomerulosclerosis

Despite frequent statements that hypertension adversely affects the cardiovascular complications of diabetes mellitus[3] most of the data have been inferential with little objective evidence adduced to support the claims Christlieb and associates described 28 diabetic patients with hypertension 27 of whom also had retinopathy this diabetic complication was much less common in normotensive patients Oakley and co workers described a series of long term diabetic patients followed for more than 40 years who had a striking absence of severe complications and concurrently had a low prevalence of high blood pressure Mogensen[3] reported a group of patients with diabetic nephropathy in whom the progression of the renal disease was slowed by antihypertensive treatment In an animal study examining the effects of renal artery clipping on the development of glomerular lesions in hypertensive diabetic rats Mauer and colleagues showed that the clipped kidneys were protected from diabetic damage while th[e] clipped kidney exposed to Goldblatt hyperte[nsion] developed diabetic alterations Similarly a [clini]cal case report" documented the ab[s]ence o[f dia]betic glomerulopathy in a hypertensive di[abetic] patient with unilateral renal artery ste[nosis] whereas the unprotected kidney had [typical] diabetic changes The present report [...] specifically suggest that hypertension ma[y be] causally related to diabetic cardiomyopathy

The clinical features of the HD patients [were] remarkably similar They were mo[st]ly [long] standing insulin dependent diabetics with [...] disease Despite the absence of signif[icant] obstructive large coronary artery disease [...] patients had severe aortic atherosclerosis [...] five had peripheral vascular disease nec[essitating] amputation The reason for the discord[ance] between the coronary and extracardiac vess[els is] unknown and it requires further study The [...] patients all had long histories of congestive [heart] failure which in most cases was thought to [be a] consequence of ischemic coronary artery dis[ease]



Fig 7 The intramyocardial artery has a widely patent lumen but the wall of the vessel is focally replaced by collagen and other stains demonstrate PAS-positive material and elastic tissue proliferation This process is characterized a vascular sclerosis in our semiquantitative analysis Concentric fibrosis cuffs the vessel and impinges on the surrounding myocardium and represents an example of perivascular fibrosis as tabulated in this study (Trichrome stain original magnification ×200)

Two patients had even been diagnosed as having myocardial infarctions yet we found no pathological evidence of old infarcts at autopsy

Pathologically there were several characteristic but non specific features of HD heart disease It is important to emphasize that the lesions described in this report are not unique to this group of patients but are frequently observed in many other types of cardiomyopathy Employing semiquantitative techniques however we were able to differentiate the alterations in hypertensive diabetic hearts from the changes observed in hypertensive diabetic or normal subjects

We believe that fibrosis is the most important functional lesion in the HD hearts Statistical analysis revealed a significant increase of interstitial fibrosis in these hearts compared to the H control group where such lesions were less common and the D and N groups where it was distinctly rare It is probable that this fibrosis contributes to the tactile sensation of stiff muscle observed grossly Although this theory is speculative this fibrosis may be sufficient to account for limited ventricular contraction producing clinical cardiomyopathy The fibrosis also appears to be related to the localization of PAS positive diastase resistant material in the myocardium In contrast to the reports of Regan and associates who found PAS positive material in human and canine hearts with diabetes mellitus and no apparent hypertension we observed no pronounced deposition in the diabetic group and only found such material in the regions of interstitial fibrosis and focal scar in the hypertensive diabetic as well as in the hypertensive hearts The similar localization of PAS positive glycoprotein and interstitial collagen suggests that the deposition of both substances has a common pathogenesis It is tempting to propose that they result from increased vascular permeability due to the combination of diabetic and hypertensive injury to small vessels however as yet no evidence exists to support this mechanism

Focal scars were also present to a significant degree in the HD hearts in comparison with the three other groups These patchy scars were generally microscopic in size, but rarely were large enough to be appreciated macroscopically They often were scattered haphazardly throughout the myocardium and this fact plus their size mitigated against their being caused by overlooked lesions in the large coronary arteries In several hearts it was possible to trace the development of scars from myocytolytic foci which progressed from acute through a healing stage of dense collagen deposition We believe that the frequent observation of myocytolysis in the HD hearts explains the frequency of the focal scars in these patients It is of interest to note that myocytolysis is a form of myocardial necrosis thought to be secondary to exogenous catecholamine administration or endogenous catecholamine excess[1] Although long term diabetics have remarkedly reduced tissue levels of norepinephrine[11] those diabetic patients with complications (retinopathy) have increased vascular reactivity to this agent [1] The role of catecholamines and other vasoactive substances in the initiation of myocardial fibrosis in hypertensive diabetics and its possible involvement in the development of cardiomyopathy require further exploration

The semiquantitative morphologic analysis in this study demonstrated that there was no significant difference in the numbers of small intramyocardial vessels with abnormalities in any of the four groups of patients This implies (but in no way is definitive) that small vessel disease is not the cause of hypertensive diabetic cardiomyopathy However subjectively it was apparent that the degree of vascular abnormality in any single vessel was more severe in the HD hearts than in the other groups Thus localized tissue ischemia may still be an important factor in the pathogenesis of this disease

The finding that severe cardiomyopathy in diabetes mellitus is related to the presence of hypertension was an unexpected result of our study Initially our objective was to examine a consecutive autopsy series of patients with diabetes mellitus congestive heart failure and minimal coronary artery disease Only in retrospect did it become apparent that all nine patients selected for inclusion were hypertensive Other studies of diabetic cardiomyopathy have explicitly excluded hypertensive patients from analy and therefore this association has probably b overlooked That hypertension alone can account for the severity of the lesions we obser is confirmed by the quantitative differen between the H and HD groups Similarly norr tensive diabetics showed only minimal card changes The absence of pathological card alterations in patients with long standing norr tensive diabetes mellitus clearly separates study from previous reports of diabetic carc myopathy We have no explanation for this crepancy

Several potential limitations of the pres study should be considered The differences mean heart weight between the four groups m provide an alternative explanation for the sev ty of the degenerative lesions in the hypertensi diabetics On the other hand the overlap betw heart weights in the HD and H group provide means to evaluate the significance of this para eter Though the groups are small a compari of the heart weights in the HD and H patients well as within the entire HD group (see Table I suggest that the severity of the lesions does r correlate with heart weight Obviously howev this is an important question which will requ study of larger numbers of patients An additio consideration concerns the nature of the cont groups employed in this study Ideally an app priate control group for the hypertensive diabe patients with cardiomyopathy would have bee series of hypertensive patients with simi degrees of congestive heart failure In searchi for such a group we were limited by in sufficie numbers of patients without epicardial corona artery disease who otherwise fulfilled our criter Therefore further studies will be required establish if hypertensive patients with conge ti heart failure have myocardial degeneration in lar to hypertensive diabetic individuals with fa ure

It may be argued that observer bias or inappr priate controls could account for the differenc between our study and others This would difficult to refute if we had not had the opport nity to carry out a series of quantitative morph logical investigations in an animal model of t human disease We analyzed rats made di betic with streptozotocin and hyperten ne wi unilateral renal artery clip and compared the animals with normotensive controls normote

sive diabetics and non diabetic hypertensives The range of abnormalities occurring within a brief 8 week period was strikingly similar to human HD cardiomyopathy reported herein and established that the combination of hypertension and diabetes mellitus is associated with the development of significant interstitial fibrosis and focal scars Observations regarding deposition of PAS positive material myocytolysis and small vessel disease were identical to those described in the present study These experiments provide preliminary confirmation for our contention that the combination of diabetes mellitus and hypertension produces significant myocardial morphological damage The similarity of the animal model to the human disease suggests that in the future the rat hypertensive diabetic model will enable us to explore the pathogenesis of this form of cardiomyopathy in more detail

Summary

The existence of a specific cardiomyopathy secondary to diabetes mellitus is controversial During a 2 year period we had the opportunity to examine nine diabetic patients at autopsy who had clinically severe congestive heart failure and minimal extramural coronary artery atherosclerosis Unexpectedly all nine patients were found to be hypertensive Accordingly we initiated a detailed study of the clinical and morphological features of this group and compared the findings to age matched autopsied subjects with either isolated hypertension isolated diabetes mellitus or no heart disease

The study of the hypertensive diabetic hearts revealed severe interstitial fibrosis focal or confluent scars and extensive myocytolytic activity Comparison with the diabetic hypertensive and normal groups showed statistically significant differences in regard to the degree of interstitial and focal scarring and the presence of myocytolysis Only the hypertensive group had minimal interstitial scarring There were no statistical differences in the small vessel changes between the four groups although subjectively the hypertensive and hypertensive diabetic patients had more severe disease

It is concluded that the association of diabetes mellitus and hypertension in the absence of significant coronary artery atherosclerosis may lead to a severe cardiomyopathy Although the etiology of myocardial failure in this syndrome is uncertain the degree of myocardial fibrosis and the frequency of myocytolytic lesions possibly related to catecholamine hypersensitivity are potential explanations Several studies suggesting that hypertension has adverse consequences in diabetes as well as an animal model of hypertensive diabetic cardiomyopathy support our conclusion that cardiomyopathy associated with diabetes mellitus is a specific entity which may be secondary to the combined effects of diabetes and hypertension on the myocardium

We appreciate the excellent secretarial assistance of Ms Toni Maio

REFERENCES

1 Ostrander L D Jr Francis T Jr., Hayner N S Kjelsberg M O and Epstein F H The relationship of cardiovascular disease to hyperglycemia Ann Intern Med 62 1188 1965
2 Kannel W B Hjortland M and Castelli, W P Role of diabetes in congestive heart failure The Framingham study Am J Cardiol 34 29 19 4
3 Stearns S Schlesinger M J and Rudy A Incidence and clinical significance of coronary artery disease in diabetes mellitus Arch Intern Med 80 463 1947
4 Clawson B J and Bell E T Incidence of fatal coronary disease in non-diabetic and in diabetic persons Arch Pathol 48 105 1949
5 Bell, E T A postmortem study of vascular disease in diabetics, Arch Pathol 53 444 1952
6 Liebow I M., Hellerstein H K and Miller M Arteriosclerotic heart disease in diabetes mellitus A clinical study of 383 patients Am J Med 18 438 1955
7 Vihert A M Zhdanov V S and Matova E E Atherosclerosis of the aorta and coronary vessels of the heart in cases of various diseases J Atheroscler Res 9 179 1969
8 Crall F V Jr and Roberts W C The extramural and intramural coronary arteries in juvenile diabetes mellitus Analysis of nine necropsy patients aged 19 to 38 years with onset of diabetes before age 15 years Am J Med 64 221 1978
9 Sohar E Ravid, M Benshaul Y Reshef T and Gafni J Diabetic fibrillosis A report of three cases, Am J Med 49 64 1970
10 Rubler S Dlugash, J Yuceoglu Y Z Kumral, T., Branwood, A W and Grishman A New type of cardiomyopathy associated with diabetic glomerulosclerosis Am J Cardiol 30 595 1972
11 Hamby R I Zoneraich, S and Sherman L Diabetic cardiomyopathy J.A.M.A 229 1749 1974
12 Ragan T J Ahmed S S Levinson G E Oldewurtel, H A Ahmad M R Haider B and Lyons M M Cardiomyopathy and regional scar in diabetes mellitus Trans Assoc Am Physicians 83 217 1975
13 Seneviratne B I B Diabetic cardiomyopathy The preclinical phase Br Med J 1 1444 1977
14 Regan T J Lyons M M Ahmed S S Levinson, G E Oldewurtel H A Ahmad M R and Haider B Evidence for cardiomyopathy in familial diabetes mellitus, J Clin Invest 60 885 1977
15 Regan T J and Weisse A B The question of cardiomyopathy in diabetes mellitus (editorial) Ann Intern Med 89 1000 19 8

16 D Elia J A Weinrauch L A and Healy R W Myocardial dysfunction without coronary artery disease in diabetic renal failure Am J Cardiol 43 193 1979
17 Blumenthal H T Alex M and Goldenberg S A study of lesions of the intramural coronary artery branches in diabetes mellitus Arch Pathol 70 27 1960
18 Ledet T Histological and histochemical changes in the coronary arteries of old diabetic patients Diabetologia 4 268 1968
19 Ledet T Diabetic cardiopathy Quantitative histological studies of the heart from young juvenile diabetics Arch Pathol Microbiol Scand 84 421 1976
20 Regan T J Ettinger P O Khan M I Jesrani M U Lyons M M Oldewurtel H A and Weber M Altered myocardial function without ischemia in dogs Circ Res 35 222 1974
21 Haider B Ahmed S S Moschos C B, Oldewurtel H A and Regan T J Myocardial function and coronary blood flow response to acute ischemia in chronic canine diabetes Circ Res 40 577 1977
22 Balme H W and Cole L The heredity of hypertension in diabetes mellitus Q J Med 20 335 1951
23 Freedman P Moulton R and Spencer A G Hypertension and diabetes mellitus Q J Med 27 293 1958
24 Pell S and D Alonzo C A Some aspects of hypertension in diabetes mellitus J A M A 202 104 1967
25 Christlieb A R Diabetes and hypertensive vascular disease Mechanisms and treatment Am J Cardiol 32 592 1973
26 Christlieb A R Nephropathy the renin system and hypertensive vascular disease in diabetes mellitus Cardiovasc Med 3 417 1978
27 Goodkin G Mortality factors in diabetes J Occup Med 17 716 1975
28 McMillan D E Diabetic angiopathy—its lessons in vascular physiology AM HEART J 96 401 1978
29 Weinrauch L A D'Elia J A Leland S Jr Healy R W Goldstein H H Libertino J A Takacs F J and Bradley R F Coronary artery disease in diabetic nephropathy Effect on management of severe renal insufficiency Cardiovasc Med 3 1079 1978
30 Factor S M Intramyocardial small vessel disease in chronic alcoholism AM HEART J 92 561 1976
31 Colquhoun D Numerical and rank measurements Two independent samples Chapt 9 Lectures on Biostatistics An Introduction to Statistics Applications in Biology and Medicine Oxford 1971 Clarendon Press
32 Scott R C Diabetes and the heart (Editorial) AM HEART J 90 283 1975
33 Kannel W B and McGee D L Diabetes and cardiovascular risk factors The Framingham study Circulation 59 8 1979
34 Christlieb A R Renin angiotensin and norepinephrine in alloxan diabetes Diabetes 23 962 1974
35 Christlieb A R Janka H U Kraus B Gleason R E Icasas-Cabral E A Aiello L M Cabral B V and Solano A Vascular reactivity to angiotensin II and to norepinephrine in diabetic subjects Diabetes 25 5? 1976
36 Christlieb A R Kaldang, A and D'Elia J A Plasma renin activity and hypertension in diabetes mellitus Diabetes 25 969 1976
37 Oakley W G Pyke D A Tattersall R B and Watkins P J Long term diabetes A clinical study of 9? patients after 40 years Q J Med 43 145 1974
38 Mogensen C E Progression of nephropathy in long term diabetics with proteinuria and effect of initial anti hypertensive treatment Scand J Clin Lab Invest 36 383 1976
39 Mogensen C E High blood pressure as a factor in the progression of diabetic nephropathy Acta Med Scand (Suppl 602) 29 1977
40 Mauer S M Steffes M W Azar S Sandberg S K and Brown D M The effects of Goldblatt hypertension on development of the glomerular lesions [illegible] mellitus in the rat Diabetes 27 738 1978
41 Berkman J and Rifkin H Unilateral nodu[illegible] glomerulosclerosis (Kimmelstiel Wilson) R[illegible] case Metabolism Clin Exp 22 715 1973
42 Baroldi G Different types of myocardial [illegible] coronary heart disease a pathophysiologi[illegible] their functional significance AM HEART [illegible] 1975
43 Neubauer B and Christensen N J Nore[illegible] epinephrine and dopamine contents of the c[illegible] lar system in long term diabetics Diabetes 2[illegible]
44 Christensen N J Plasma catecholamines in [illegible] diabetics with and without neuropathy and i[illegible] sectomized subjects J Clin Invest 51 779 1[illegible]
45 Factor S M Bhan R Minase T Wolinsk[illegible] Sonnenblick E H Morphological features o[illegible] sive diabetic heart disease in the rat (Abstr) [illegible] 37 489 1978
46 Bhan R Factor S M Minase T Wolinsk[illegible] Sonnenblick E H Ultrastructural features o[illegible] sive diabetic cardiomyopathy in the rat (Ab[illegible] Proc 37 489 1978

Technetium 99m stannous pyrophosphate myocardial scintigrams in pericardial disease*

Harold G Olson M D**
Kenneth P Lyons M D **
Wilbert S Aronow M D****
John Kuperus M S ***
Joan R Orlando M D**** *
Harris J Waters B S ***
Long Beach and Irvine Calif

Previous studies in experimental animals and man have demonstrated that Tc PYP myocardial scintigraphy is a very sensitive technique for diagnosing acute myocardial infarction[1-11] However recent reports indicate that abnormal myocardial scintigrams may occur in clinical conditions other than acute myocardial infarction such as ventricular aneurysm[1] stable and unstable angina pectoris old myocardial infarction slow ongoing myocardial necrosis[1] following high energy transthoracic cardioversion metastatic disease of the heart myocardial contusion myocardiopathy valvular calcification experimental endocarditis and even in apparently normal hearts[1]

Since acute pericarditis may mimic many of the clinical features of acute myocardial infarction including chest pain nonspecific electrocardiographic changes and transient serum enzyme abnormalities the present investigation was undertaken to assess ^{99m}Tc PYP myocardial scintigraphy in patients with acute and chronic pericardial disease The results from this study are reported here

Methods

The study population consisted of 38 patients 35 with acute pericarditis and three with chronic constrictive pericarditis All the patients were males ranging in age from 22 to 67 years (mean 48 years) Acute pericarditis was diagnosed by typical history and the presence of a two or three component pericardial friction rub Chronic constrictive pericarditis was diagnosed by history physical examination and findings at cardiac catheterization None of the patients had unstable angina pectoris recent high energy transthoracic cardioversion a calcified cardiac valve or were in congestive heart failure Seven of the patients had a documented myocardial infarction five or more weeks prior to scintigraphy To differentiate a positive scintigram related to acute pericarditis from a persistently positive scintigram due to myocardial infarction a negative follow up scintigram was required in all patients with prior myocardial infarction and a positive scintigram during acute pericarditis

Technetium 99m myocardial scintigrams were obtained in all 35 patients with acute pericarditis 3 0 ± 1 2 days after the onset of symptoms or the

From the C dio ascular Sect on Medi l S rvice nd th Nu l r Medic ne Servi Long B h V t ans Administrat on Ho pit l, nd the Uni rsity f Californi Irvin

Rec ed f p blicat n N 15 19 8

A pted f publi tion Mar h 9 19 9

Repri t eq ests Harold G Olson M D Director C onary Care Unit V t Adm n tr t on Ho pit l Long Be h, Calif 9082.

*Prese ted in part at th Fift th Sci tific Sess n of th Ameri H rt Associat n N ember 19— Miam Bea h Fl rid

Di ect C ro ary C Un t Long Beach VAH Assist nt Professor of Med in Univers ty f Californ Irvin

Ch f N lear Med c ne Serv e Long Bea h VAH Assistant Professo f R diologi l Sciences Uni rsity of C lif rnia Irvine

Ch f C rdio asc l Secti Long Bea h VAH Professo of Medicin V e Chi f C rdiovascular D ision d Chi f Ca d o ascular Resea h Univ rsity of C liforn Irvin

R d pharm ist Long B ach VAH

Chief H rt Station Long Be ch VAH Assistant Professor of Med ci Uni ersity of C l f nia Irvine

Medical St dent U ers ty of C liforn Lo Ang les.

0002 8 03/80/040459 + 09$00 90/0 © 1980 The C V Mosby Co

Table I Etiologies of acute and chronic pericarditis and interpretation of myocardial scintigrams

Etiologic diagnosis	*Number of patients*	*Positive scan (no)*	*Positive scan (%)*
Acute pericarditis	35	13	37
Idiopathic	11	6	55
Viral	1	0	0
Bacterial	2	1	50
Tuberculosis	1	1	100
Connective tissue disease	3	0	0
Uremia	5	0	0
Postmyocardial infarction syndrome	6	2	33
Metastatic neoplasm	4	1	25
Unrecognized myocardial infarction	1	1	100
Post thoracotomy syndrome	1	1	100
Chronic constrictive pericarditis	3	1	33
Idiopathic calcific	1	1	100
Idiopathic noncalcific	1	0	0
Post traumatic	1	0	0

Table II Characteristics of Tc PYP myocardial scintigrams obtained in 35 patients with acute pericarditis

Number of patients	*R*	*R*	*D*	*D*	*D*	*0*
35	1	5	0	7	9	13

Abbreviations R = regional 3+ activity R = regional 2+ activity D = diffuse 3+ activity D = diffuse 2+ activity D = diffuse 1+ activity 0 = no activity = negative scintigram.

appearance of their pericardial friction rub and one day prior to cardiac catheterization in the three patients with chronic constrictive pericarditis Eight of the 35 acute pericarditis patients (23%) and one of the three chronic constrictive pericarditis patients (33%) had a follow up scintigram 6 1 ± 2 3 weeks after their initial study

Myocardial imaging was performed two hours after the injection of 20 mCi of Tc PYP containing less than 0 15 mg of tin Chromatography as previously described was performed prior to each study In all studies free technetium was less than 1% and reduced hydrolyzed technetium was less than 5% Repeat imaging at four hours after injection was performed in all patients with suspected persistent blood pool activity Myocardial images were obtained in three views left anterior 45 degree left anterior oblique and left lateral projections Myocardial scintigrams were recorded using either a Searle Pho Gamma HP scintillation camera with a Divcon collimator in the converging mode or a Searle Pho Gamma V scintillation camera with a high resolution collimator Each view contained 500 000 counts with the Divcon collimator or 400 000 counts with the high resolution collimator with a 20% window and a photo peak centered on 140 keV Serial studies on individual patients were performed by the same camera and collimator

The myocardial scintigrams were interpreted using our grading system Zero activity indicated no myocardial activity An intensity of 1+ was assigned for myocardial activity less than that of the ribs 2+ for activity equal to or greater than rib activity and 3+ for activity equal to or greater than sternal activity A scintigram of 2+ or greater activity was considered abnormal Using this grading system of 361 patients with documented acute myocardial infarction treated at our hospital 331 (92%) had positive scintigrams obtained during their infarction while one of 46 patients (2%) without clinical heart disease had a positive scintigram

Myocardial scintigrams were graded according to the distribution of activity Regional uptake was considered when activity was localized to an anatomical wall of the heart Diffuse uptake was assigned when anatomical location was indeterminant Myocardial scintigrams were interpreted by two independent observers without knowledge of the patients diagnosis or clinical status There was complete agreement between the two observers in all the myocardial scintigrams interpreted

During their hospitalization all 35 patients

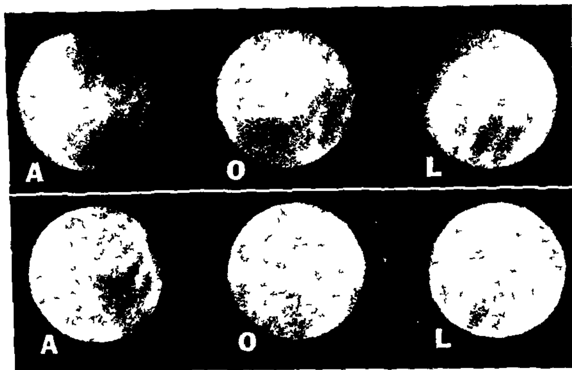


Fig. 1. *The upper panel* shows a positive myocardial scintigram with a 3+ regional abnormality in a patient with postmyocardial infarction pericarditis. The patient had an uncomplicated myocardial infarction 5 weeks prior to the onset of acute pericarditis. *The lower panel* shows a negative follow-up myocardial scintigram 6 weeks after acute pericarditis. A = anterior; O = 45 degrees left anterior oblique; L = left lateral projections.

with acute pericarditis had serial 12 lead electrocardiograms, blood analyzed for serum enzymes CK, CK-MB, SGOT, LDH, and HBD, and echocardiograms. Diagnosis of acute pericarditis by electrocardiography was considered certain if there was diffuse concave ST segment elevation in epicardial leads followed by evolutionary ST-T wave changes without development of new Q waves.[3] Pericardial effusion was diagnosed by echocardiography or by pericardicentesis.

The data are presented as the mean ± the standard deviation. The chi square test was used to test for significant differences.

Results

Scintigraphic findings in acute pericarditis. The etiologies of the acute pericarditis and the interpretation of the myocardial scintigrams are shown in Table I. Of the 13 patients with positive scintigrams, six (46%) had a regional abnormality and seven (54%) had a diffuse abnormality (Table II). One patient had a 3+ intensity myocardial scintigram.

Fig. 1 illustrates a positive myocardial scintigram with a regional abnormality in a patient with postmyocardial infarction pericarditis. The patient had an uncomplicated myocardial infarction 5 weeks prior to onset of acute pericarditis. The lower panel shows a negative follow-up scintigram in this patient 6 weeks after acute pericarditis. Fig. 2 illustrates a diffuse scintigraphic abnormality during acute idiopathic pericarditis.

Table III correlates the electrocardiographic features, elevation of CK, elevation of CK plus CK-MB serum enzymes, and the presence or absense of pericardial effusion with the incidence of positive scintigrams during acute pericarditis. As indicated, patients with acute pericarditis and classic electrocardiographic changes of acute pericarditis were significantly more likely to have positive myocardial scintigrams compared to patients without these electrocardiographic changes. Two patients had transient atrial fibrillation during acute pericarditis and both had positive myocardial scintigrams.

Of the eight patients with acute pericarditis who had follow-up scintigraphy, all five patients with initially positive studies had negative studies at follow-up 6.2 ± 1.3 weeks after initial scintigraphy (Fig. 1). Of the three patients who had

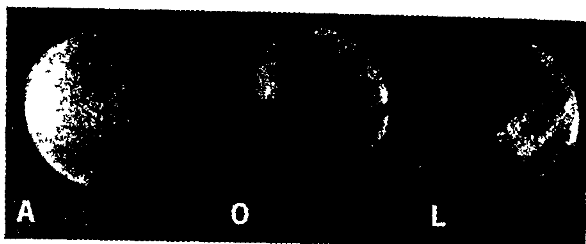


Fig 2 A positive myocardial scintigram with a 2+ diffuse abnormality in a patient with acute idiopathic pericarditis A = anterior O = 45 degree left anterior oblique L = left lateral projections

Table III Electrocardiographic features CK and CK MB elevation and presence or absence of pericardial effusion correlated with the results of myocardial scintigraphy in 35 patients with acute pericarditis

Parameter	*Number of patients*	*Positive scan*	
		No	*%*
Electrocardiogram			
Consistent with acute pericarditis	18	10	56
Not consistent with acute pericarditis	17	3	18
Acute inferior infarction	1	1	100
Old anterior infarction	2	0	0
Old inferior infarction	2	1	50
Left ventricular hypertrophy	3	1	33
RBBB and LAH	1	0	0
Low voltage and nonspecific ST T wave changes	1	0	0
Nonspecific ST T wave changes	7	0	0
CK			
CK elevation	6	4	67
CK plus CK MB elevation	2	2	100
Pericardial effusion			
Present	27	8	30
Absent	8	5	63

Abbreviations RBBB = right bundle branch block LAH = left anterior hemiblock * = $P < 0.02$ compared with ECG not consistent with acute pericarditis

initially negative scintigrams all three had negative studies at follow up 6.0 ± 2.1 weeks after initial scintigraphy

Autopsy data were obtained in one patient with malignant pericarditis secondary to bronchogenic carcinoma of the lung Fig 3 shows the myocardial scintigram obtained in this patient during acute pericarditis and a histologic section of his myocardium obtained at autopsy one month later The tumor involved not only the parietal pericardium but also involved extensive areas of both the right and left ventricles

Scintigraphic findings in chronic constrictive pericarditis The etiologic basis of the patients chronic constrictive pericarditis and the results of the myocardial scintigrams are shown in Table I Only one patient with chronic constrictive pericarditis had an abnormal scintigram This patient had pericardial calcification determined by image intensification at cardiac catheterization and by

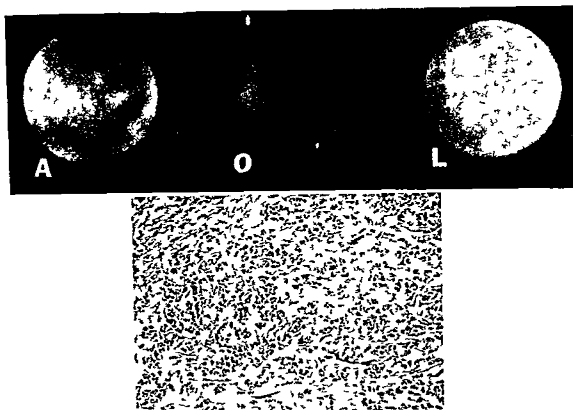


Fig 3 *The upper panel* shows a 2+ positive myocardial scintigram in a patient with acute malignant pericarditis from metastatic bronchogenic carcinoma *The lower panel* shows a histologic section of left ventricular myocardium from this patient The normal architecture of the myocardium is completely disrupted by large sheets of malignant cells showing extreme variation of size and shape There is interstitial edema fibrosis and varying degrees of myocardial necrosis (Hematoxylin and eosin stain original magnification ×10)

histologic sections of pericardium removed at surgery Fig 4 shows serial myocardial scintigrams and a histologic section of pericardium removed at surgery in this patient The other two patients with negative myocardial scintigrams had only thickened noncalcific fibrotic pericardium removed at surgery

Discussion

The results from the present study indicate that ^{m}Tc PYP myocardial scintigrams obtained in patients with acute pericarditis or chronic constrictive pericarditis may be abnormal Thirteen of 35 patients (37%) with acute pericarditis and one of three patients (33%) with chronic constrictive pericarditis had positive scintigrams The scintigraphic abnormality observed was generally a 2+ regional or diffuse pattern which is similar to that reported in patients with acute nontransmural myocardial infarction [18] One patient had a myocardial scintigram which was interpreted as acute transmural inferior wall myocardial infarction Thus false positive scintigrams for myocardial infarction may occur in patients with pericardial disease

Traditionally acute pericarditis has been considered an inflammation of the parietal layer of the pericardium epicardium or both with the formation of exudates within the pericardial cavity The exudates have been classified as fibrinous serous purulent hemorrhagic and cholesterol [34] The extent of inflammation and the nature of the exudates are determined by the etiologic agent With healing there is reabsorption of the exudates and return of the pericardium or epicardium to normal structure [34] In some patients inflammation continues and there is organization of the exudate with fusion of the parietal and visceral layers of the pericardium The pericardium may become diffusely thickened

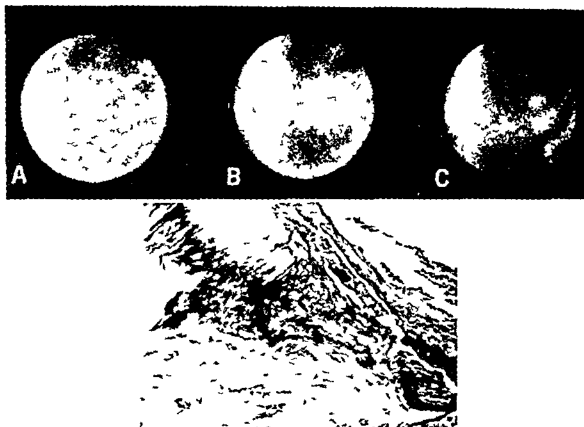


Fig 4 Serial myocardial scintigrams in the patient with chronic constrictive pericarditis and a histologic section of his pericardium removed at surgery *The upper panel* shows *A* Preoperative 2+ positive myocardial scintigram *B* 3+ positive myocardial scintigram obtained 5 days after pericardiectomy consistent with the clinical diagnosis of a perioperative myocardial infarction and *C* a 1+ negative myocardial scintigram at follow up 6 weeks after pericardiectomy *The lower panel* shows calcification of the parietal pericardium Dark calcium spicules stand out sharply in contrast to the lightly staining fibrotic pericardium (Hematoxylin and eosin stain original magnification ×10)

and fibrotic Similar changes may occur in the epicardium These changes may result in cardiac constriction Calcification of the pericardium may be a late manifestation of the inflammatory process

The mechanism for positive scintigrams in our patients with pericardial disease is only speculative In experimental acute myocardial infarction ^{99m}Tc PYP has been shown to accumulate within the zone of infarction within 12 hours after the onset of injury reaching a peak within 72 hours and then gradually resolving Whether the radionuclide combines with soluble or insoluble forms of tissue calcium which increases during acute infarction or to macromolecules of denatured protein remains controversial The importance of the amount of necrotic tissue and delivery of the radionuclide by blood flow to the zone of injury for scintigraphic detection of myocardial necrosis have previously been e sized[41,43] Finally convincing experimenta indicate that myocardial uptake of ^{99m}Tc l always associated with histologic evide myocardial necrosis [3,42,4]

Thus it is reasonable to suggest several p mechanisms for abnormal scintigrams in p with pericardial disease These mech include radionuclide accumulation with pericardium sequestration of the radionuc the exudative process within the pericardia ty and myocardial uptake

The data suggest that pericardial uptake radionuclide was operative in the patient chronic calcific pericarditis while myoc uptake was the major determinant for p scintigraphy in patients with acute perica Of the three patients with chronic consti pericarditis a positive scintigram occurred o

the patient with a calcified pericardium Further more pericardiectomy resulted in normalization of this patient s scintigram (Fig 4) Thus the presence of calcium within the pericardium most likely concentrated the bone seeking radionuclide and was probably responsible for the abnormal scintigram

The incidence of myocardial involvement myo carditis in the clinical setting of acute pericarditis is unknown Certainly the etiology of acute pericarditis is an important determinant of myo cardial involvement For example studies indi cate that myocarditis is not uncommon in viral Coxsackie B pericarditis [7] Criteria for the clin ical diagnosis of myocarditis in the setting of acute pericarditis include ventricular failure manifested by ventricular dilatation new cardiac rhythm or conduction disturbances presence of cardiospecific serum enzymes as CK MB or the presence of distinctive evolutionary electrocar diographic changes of acute pericarditis which most likely represent superficial myocarditis [3, 3] None of our patients had ventricular failure The two patients with transient atrial fibrillation and the two other patients with CK plus CK MB serum enzyme elevation had positive myocardial scintigrams Of the 13 patients with positive myocardial scintigrams during acute pericarditis ten (77%) had classical evolutionary electrocar diograms of acute pericarditis Additionally the positive scintigram in the patient with unrecog nized myocardial infarction probably represented accumulation of the isotope in the area of infarc tion The one patient with proven myocardial involvement with carcinoma also had a positive scintigram Other investigators have also noted positive myocardial scintigrams in patients with invasive carcinoma of the myocardium Al though the data suggest that abnormal scinti grams during acute pericarditis are due predomi nantly to radionuclide sequestration in concomi tantly involved myocardium the contribution of radionuclide accumulation within the involved pericardium and associated exudate will require further study

Abnormal myocardial scintigrams in normal hearts have been previously reported [10] Generally the scintigraphic abnormality is a diffuse pattern rather than a regional pattern In our experience this scintigraphic abnormality in normal hearts is due to blood pool activity which is the result of poor preparation of the radiopharmaceutical (ex cessive tin free or reduced hydrolyzed techne tium) or delayed clearance of the radionuclide Documentation of binding of ^{99m}Tc PYP prior to each study by chromatography delayed imaging to four hours after injection and comparison with blood pool studies in the same patients eliminate confusion with regard to false positive blood pool scans [7, 15]

Serial studies of the eight patients with acute pericarditis and one patient with chronic constric tive pericarditis support the concept that the abnormal images observed in this study represent evidence of pathological involvement of both the pericardium and myocardium At follow up all five patients with abnormal scintigraphy during acute pericarditis (three diffuse pattern and two regional pattern) were negative Similarly all three patients with initial negative studies had negative follow up studies The one chronic con strictive pericarditis patient with an abnormal scintigram had a negative scintigram following pericardiectomy

Acute pericarditis is traditionally diagnosed by the presence of chest pain pericardial friction rub and electrocardiographic changes The true incidence of this disorder is unknown since many patients may not have a pericardial friction rub or electrocardiographic changes It is possible that some patients admitted to coronary care units with chest pain mimicking acute myocardial infarction who have positive ^{99m}Tc PYP myocar dial scintigrams may have unsuspected acute pericarditis Thus one must rule out the diagnosis of acute pericarditis in patients with positive ^{99m}Tc PYP myocardial scintigrams before con cluding that an acute myocardial infarction is present

Summary

Technetium 99m stannous pyrophosphate (^{99m}Tc PYP) myocardial scintigrams were ob tained in 35 acute pericarditis and in three chronic constrictive pericarditis patients Thir teen of 35 acute pericarditis patients (37%) and one of three chronic constrictive pericarditis patients (33%) had abnormal scintigrams (a dif fuse pattern in eight patients and a regional pattern in six patients) Of the 17 acute pericardi tis patients with classic ST segment changes of acute pericarditis 10 (56%) had abnormal scinti

grams compared to three of 17 patients (18%) without these ECG changes (P < 0 02) These data indicate that pericardial disease may cause an abnormal scintigram Therefore one must rule out pericardial disease before concluding that a positive scintigram is due to acute myocardial infarction

The authors greatly appreciate the technical assistance of Marion Levens Robert Walker and Jack Newby and the secretarial assistance of Mary Ellen Dunchak

REFERENCES

1 Bonte F J Parkey R W Graham K D Moore J G and Stokley E M A new method for radionuclide imaging of myocardial infarcts Radiology 100 473 1974
2 Parkey R W Bonte F J Meyer S L Atkins J M Curry G C Stokely E M and Willerson J T A new method for radionuclide imaging of acute infarction in humans Circulation 50 540 1974
3 Willerson J T Parkey R W Bonte F J Meyer S L Atkins J M and Stokely E M Technetium stannous pyrophosphate myocardial scintigrams in patients with chest pain of varying etiology Circulation 51 1046 1975
4 Willerson J T Parkey R W Bonte F J Meyer S L and Stokely E M Acute subendocardial myocardial infarction in patients Its detection by technetium[99m] stannous pyrophosphate myocardial scintigrams Circulation 51 430 1975
5 McLaughlin P Coates G Word D Cradduck T and March J Detection of acute myocardial infarction by technetium 99m polyphosphate Am J Cardiol 35 390 1975
6 Stokley E M Buja L M Lewis S E Parkey R W Bonte F J Harris R A and Willerson J T Measurement of acute myocardial infarcts in dogs with [99m]Tc stannous pyrophosphate scintigrams J Nucl Med 17 1 1976
7 Berman D S Amsterdam E A Hines H H Salel A F Barley G J De Nardo G L and Mason D T New approach to interpretation of technetium 99m pyrophosphate scintigraphy in detection of acute myocardial infarction Am J Cardiol 39 341 1977
8 Cowley M J Mantle J A Rogers W J Russell R O Jr Rackley C E and Logic J R Technetium 99m stannous pyrophosphate myocardial scintigraphy Reliability and limitation in assessment of acute myocardial infarction Circulation 56 19_ 19_
9 Platt M R Parkey R W Willerson J T Bonte F J Shapiro W and Sugg W L Technetium stannous pyrophosphate myocardial scintigrams in the recognition of myocardial infarction in patients undergoing coronary artery revascularization Ann Thorac Surg 21 311 1976
10 Klausner S C Botvinick E H Shames D Ullyot D J Fishman N H Roe B B Ebert P A Chatterjee K and Parmley W W The application of radionuclide infarct scintigraphy to diagnose perioperative myocardial infarction following revascularization Circulation 56 173 1977
11 Lyons K P Olson H G Kuperus J Stemmer E A and Aronow W S Correlation of Tc pyrophosphate myocardial scintigraphy and the result of coronary artery bypass surgery J Nucl Med 19 1116 1978
12 Holman B L Lesch M and Alpert J S Myocardial scintigraphy with technetium 99m pyrophosphate during the earlier phase of acute myocardial infarction Am J Cardiol 41 39 1978
13 Sharpe D N Botvinick E H Shames D M Schiller N B Massie B M Chatterjee K and Parmley W W The noninvasive diagnosis of right ventricular infarction Circulation 57 483 1978
14 Ahmad M Dubiel J P Verdon T A and Martin R H Technetium stannous pyrophosphate myocardial imaging in patients with and without ventricular aneurysm Circulation 53 833 1976
15 Mason J W Myers R W Alderman E L Stinson E B Goris M L and Kriss J P Technetium 99m pyrophosphate myocardial uptake in patients with stable angina pectoris Am J Cardiol 40 1 1977
16 Donsky M S Curry G C Parkey R W Meyer S L Bonte F J Platt M R and Willerson J T Unstable angina pectoris clinical angiographic and myocardial scintigraphic observations Br Heart J 38 257 1976
17 Olson H Lyons K Aronow W and Waters H Identification of high risk unstable angina patients for mortality and myocardial infarction Circulation 55 and 56(Suppl III) III 173 1977
18 Olson H G Lyons K P Aronow W S Brown W T and Greenfield R S Follow up technetium[99m] stannous pyrophosphate myocardial scintigrams after acute myocardial infarction Circulation 56 181 1977
19 Cowley M J Kawamura K Karp R B Mantle J A Logic J R Rogers W J Russel R O Jr Rackley C E and James T N Persistently positive [99m]Tc polyphosphate myocardial scintigrams after acute infarction Angiographic histochemical and electron microscopic correlations (Abstr) Circulation 53 and 54 (Suppl II) II 76 1976
20 Buja L M Poliner L R Parkey R W Pulido J I Hutcheson D Platt M R Mills L J Bonte F J and Willerson J T Clinicopathologic study of persistently positive technetium 99m stannous pyrophosphate myocardial scintigram and myocytolytic degeneration after myocardial infarction Circulation 56 1016 1977
21 Pugh B R Buja L M Parkey R W Poliner L R Stokely E M Bonte F J and Willerson J T Cardioversion and false positive technetium 99m stannous pyrophosphate myocardial scintigrams Circulation 54 399 1976
22 DiCola V C Freedman G S Downing S E and Zaret B L Myocardial uptake of technetium 99m stannous pyrophosphate following direct current transthoracic countershock Circulation 54 980 1976
23 Olson H Lyons K Aronow W S Orlando J and Kuperus J Technetium 99m pyrophosphate myocardial scintigraphy in patients resuscitated from sudden lethal arrhythmias Clin Res 26 96A 1978
24 Harford W Weinberg M N Buja L M Parkey R W Bonte F J and Willerson J T Positive [99m]Tc stannous pyrophosphate myocardial image in a patient with carcinoma of the lungs Radiology 122 4 197_
25 Go R T Doty D B Chiu C L and Christie J H A new method of diagnosing myocardial contusion in man by radionuclide imaging Radiology 116 107 1975
26 Perez L A Hayt D B and Freeman L M Localization of myocardial disorders other than infarction with [99m]Tc labeled phosphate agents J Nucl Med 17 241 1976
27 Righetti A O'Rourke R A Schelbert H Henning H Hardarson T Daily P O Ashburn W and Ross J Jr Usefulness of preoperative and postoperative Tc 99m(Sn) pyrophosphate scans in patients with ischemic and valvular heart disease Am J Cardiol 39 43 1977

28 Jengo J A Mena I Joe S H and Criley J M The significance of calcific valvular heart disease in Tc 99m pyrophosphate myocardial infarction scanning Radiographic scintigraphic and pathologic correlation J Nucl Med 18 776 1977

29 Riba A L Downs J Thakur M L Gottschalk A Andriole V T and Zaret B L Technetium 99m stannous pyrophosphate imaging of experimental endocarditis Circulation 58 111 1978

30 Prasquier R Taradash M R Botvinick E M Shames D M and Parmley W W The specificity of the diffuse pattern of cardiac uptake in myocardial infarction imaging with technetium 99m stannous pyrophosphate Circulation 55 61 1977

31 Kuperus J and Lyons K P Chromatography of ^{99m}Tc labeled radiopharmaceuticals J Nucl Med 18 494 1977

32 Surawicz B and Lasseter K C Electrocardiogram in pericarditis Am J Cardiol 26 471 1970

33 Spodick D H Electrocardiogram in acute pericarditis Distributions of morphologic and axial changes by stages Am J Cardiol 33 470 1974

34 Scotti T M In Anderson W A D and Kissane J M editors Pathology Saint Louis 1977 The C V Mosby Company

35 Roberts W C and Spray T L In Spodick D H editor Pericardial diseases Philadelphia 1976 F A Davis Company

36 Levine H D Myocardial fibrosis in constrictive pericarditis—electrocardiographic and pathologic observations Circulation 48 1268 1973

37 Cornell S H and Rossi N P Roentgenographic findings in constrictive pericarditis Analysis of 21 cases Am J Roentgenol 102 301 1968

38 Buja L M Parkey R W Dees J M Stokely E M Harris R A, Bonte F J and Willerson J T Morphologic correlates of technetium 99m stannous pyrophosphate imaging of acute myocardial infarcts in dogs Circulation 52 596 1975

39 Buja L M Tofe A J Kulkarni P V Mukherjee A Parkey R W Francis M D Bonte F J and Willerson J T Sites and mechanisms of localization of technetium 99m phosphorous radiopharmaceuticals in acute myocardial infarcts and other tissues J Clin Invest 60 724 1977

40 Dewanjee M K and Kahn P C Mechanism of localization of ^{99m}Tc labeled pyrophosphate and tetracycline in infarcted myocardium, J Nucl Med 17 639 1976

41 Stokely E M, Buja L M Lewis S E Parkey R W Bonte F J, Harris R A Jr and Willerson J T Measurement of acute myocardial infarcts in dogs with ^{99m}Tc stannous pyrophosphate scintigrams, J Nucl Med 17 1 1976

42 Botvinick, E H Shames D Lappin H Tyberg J V Townsend R and Parmley W W Noninvasive quantitation of myocardial infarction with technetium 99m pyrophosphate Circulation 52 909 1975

43 Zaret B L DiCola V C Donabedian R K Puri S Wolfson S Freedman G S and Cohen L S Dual radionuclide study of myocardial infarction Relationships between myocardial uptake of potassium-43 technetium 99m stannous pyrophosphate regional myocardial blood flow and creatine phosphokinase depletion Circulation 53 422 1976

44 Coleman R E Klein M S, Ahmed, S A, Weiss, E S Buchholz W M and Sobel, B E Mechanisms contributing to myocardial accumulation of technetium 99m stannous pyrophosphate after coronary arterial occlusion Am J Cardiol 39 55 1977

45 Marcus, M L, Tomanek, R J Ehrhardt J C, Kerber R E Brown D D and Abboud F M Relationships between myocardial perfusion myocardial necrosis and technetium 99m pyrophosphate uptake in dogs subjected to sudden coronary occlusion Circulation 54 647 1976

46 Martonffy K Reimer K A, Henkin R E, Jennings, R B and Quinn J L Technetium 99m pyrophosphate concentration in experimental myocardial infarcts J Nucl Med 16 548 1975

47 Fletcher E and Brennan C F Cardiac complications of Coxsackie virus infection Lancet 1 913 1957

48 Sainani G S, Krompotic E and Slodki S J Adult heart disease due to Coxsackie B infection Medicine 47 133 1968

49 Smith W G Coxsackie B myopericarditis in adults Am Heart J 80 34 1970

Intravenous quinidine pharmacokinetic properties and effects on left ventricular performance in humans*

Hermann R Ochs M D
Eberhard Grube M D
David J Greenblatt M D
Elaine Woo M D
Gunther Bodem M D
Boston Mass

The antiarrhythmic properties of quinidine are well established but its effects on cardiac function are controversial In vitro studies suggest that quinidine reduces cardiac contractility [1 4] but experiments in conscious unsedated dogs demonstrate no change in contractility [5] Although the clinical use of intravenous quinidine has traditionally been considered hazardous studies from our laboratory [6] and elsewhere [7] indicate that well controlled and monitored intravenous infusions of therapeutic doses can be administered without important untoward effects The present study assessed the effects of a single intravenous dose of quinidine upon cardiac function in healthy humans as determined by echocardiography We also investigated the relation of the pharmacodynamic effects of quinidine to its pharmacokinetic properties

Methods

Quinidine administration Ten healthy volunteers aged 23 to 34 years (eight male two female) participated in the study after giving informed consent They were free of identifiable medical disease

After a baseline echocardiogram blood pr sure and electrocardiogram (ECG) were tained 300 mg of quinidine base (as the gluc ate salt*) was infused into an antecubital vein a constant rate infusion pump† over 15 minu with subjects in the supine position Venous bl samples were taken from the contralateral fo arm before and at 0 25 0 5 0 75 1 0 1 5 2 3 4 8 10 12 24 and 36 hours after the start of infusion Serum was separated and frozen u the time of assay

The echocardiogram ECG blood pressure a carotid pulse curves were taken with subjects the supine position at times indicated above a at 5 and 10 minutes after the start of the infusi Subjects remained supine until 45 minutes af the termination of infusion following which th resumed normal activities Subsequent physiol ic measurements were taken after a 5 to minute rest in the supine position

Recording techniques Echocardiograms we recorded on light sensitive paper using a st chart recorder‡ (paper speed 50 and 100 mm sec) and a Picker Echoview 80 20A ultrason scope § The ultrasound transducer 2 25 MH 1 27 cm focused at 7 5 cm with a repetition ra of 1000 impulses/sec was placed parasternally the third or fourth left intercostal space a directed posteriorly slightly laterally and inf riorly until the interventricular septum chord

From the Department of Cardiology Medizinische Universitatsklinik, Bonn West Germany and the Clinical Pharmacology Unit Massachusetts General Hospital Boston Mass

Received for publication Jan 21 19 9
Accepted for publication Feb 1 19 9

Reprint requests David J Greenblatt M D Clinical Pharmacology Unit Massachusetts General Hospital, Boston Mass 02114

Presented in part at the 80th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics Kansas City Missouri, March 22 1979

*Eli Lilly and Company Indianapolis Indiana
†Braun Melsungen West Germany
‡Honeywell
§Picker

0002-8703/80/040468 + 08$00 80/0 © 1980 The C V Mosby C

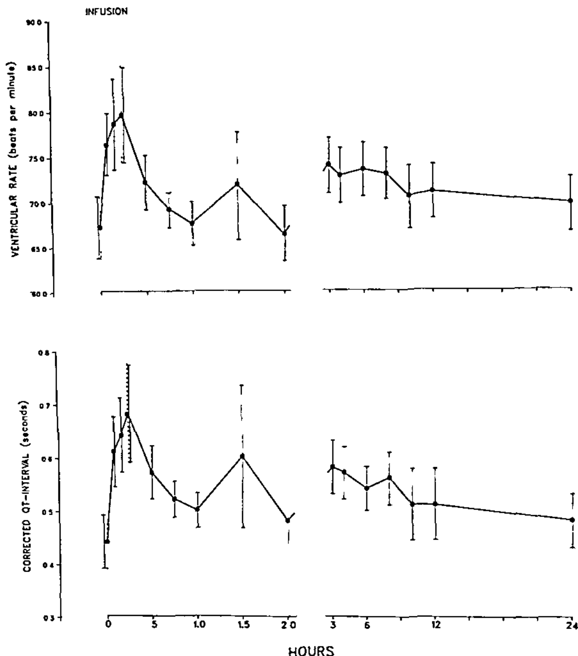


Fig 1 Electrocardiographically determined ventricular rate and corrected QT interval measured before during and after intravenous infusion of quinidine Each point is the mean (±SE) for all subjects at the corresponding time The 15 minute infusion (*vertical dashed lines*) began at time zero

tendinae of the mitral valve apparatus and the posterior wall were located The electrocardiogram and the carotid pulse tracing were recorded simultaneously

Measurement of end systolic cavity dimensions (D) and diastolic cavity dimensions (D_d) were taken from the echocardiogram End systole was defined as the smallest distance between the posterior wall and interventricular septum and end diastole was defined as the distance between those two surfaces at the time of onset of the QRS complex

Ejection time (ET) was determined using the simultaneously recorded carotid pulse tracing The width of the QRS complex and heart rate were measured on the ECG If a U wave

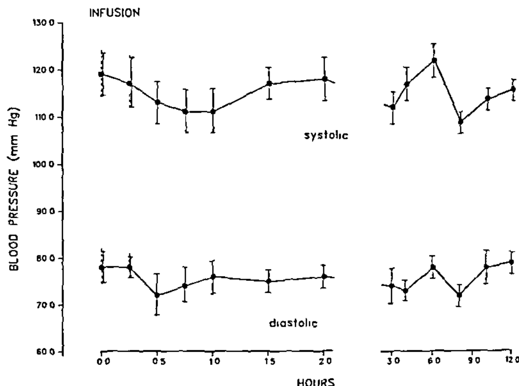


Fig 2 Systolic and diastolic blood pressure measured by cuff sphygmomanometer measured before and after intravenous infusion of quinidine Each point is the mean (+ SE) for all subjects at the corresponding time The 15 minute infusion (*vertical dashed lines*) began at time zero

occurred the maximum downslope of the T wave was extrapolated to the isoelectric line Blood pressure was measured by a cuff sphygmomanometer

The following calculations were used as indices of ventricular performance mean rate of circumferential fiber shortening

$$V_{cf} = \frac{(D_d - D_s)}{(D_d \times ET)}$$

ejection fraction

$$EF = \frac{(D_d)^3 - (D_s)^3}{(D_d)}$$

Determination of total and unbound quinidine Concentrations of quinidine in body fluids were determined by spectrophotofluorometric assay the sensitivity and specificity of which are discussed elsewhere The extent of quinidine binding to plasma protein was determined by equilibrium dialysis

Pharmacokinetic and statistical analysis The time course of total and unbound serum quinidine concentrations after intravenous infusion were analyzed by computer using weighted nonlinear least squares regression analysis Data points for each subject were fitted to a bie nential function of the form

$$C = Ae^{-\alpha t} + Be^{-\beta t}$$

where C is the serum quinidine concentratic time t after the end of the infusion A and I hybrid intercept terms and the exponer and β are hybrid rate constants After co tion for the infusion period, the fitted funct were used to calculate the following pharmac netic variables volume of the central comp ment (V_1) total volume of distribution apparent distribution half life ($t_{1/2\alpha}$) appa elimination half life ($t_{1/2\beta}$) and total c ance [14 15]

The relation of changes in pharmacodyn variables measured at 0 25 0 5 0 75 and 1 0 h after the start of the infusion to total unbound serum quinidine levels determine the corresponding times was assessed by li regression analysis

Results

Pharmacodynamics

Subjective effects Two subjects noted n congestion developing during the quinidine i sion No other subjective changes were repor

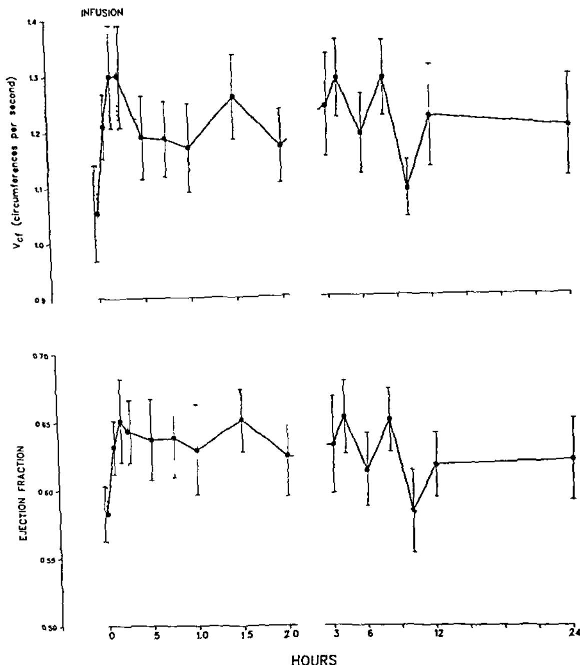


Fig 3 Echocardiographically determined mean rate of circumferential fiber shortening (V_{cf}) and ejection fraction measured before during and after intravenous infusion of quinidine Each point is the mean (±SE) for all subjects at the corresponding time The 15-minute infusion (*vertical dashed lines*) began at time zero

Electrocardiographic effects Intravenous quinidine produced a transient increase in heart rate and prolongation of the corrected QT interval (QTc) (Fig 1) These changes reverted to or near the pretreatment baseline level following termination of the infusion (Fig 1) No significant changes occurred in QRS duration

Cardiac function Intravenous quinidine produced no significant changes in blood pressure (Fig 2) V_{cf} and EF did not decrease but rather increased significantly over baseline during the quinidine infusion (Figs 3 and 4) These changes reverted partially toward the pretreatment condition shortly after the termination of the infusion However considerable variation in these measures was observed over time during the 24 hours after the termination of the infusion

Pharmacokinetics Table I summarizes phar

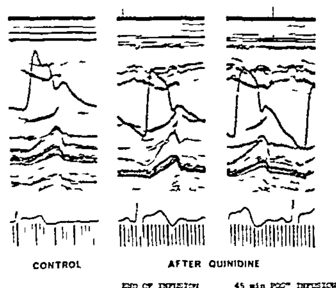


Fig 4 Echocardiogram and simultaneous carotid pulse tracing from a representative subject in the control state prior to the quinidine infusion (*left*) just at the end of the infusion (*middle*) and 45 minutes after the end of the infusion (*right*)

macokinetic values based on analysis of total and unbound quinidine concentrations for all subjects The mean per cent of serum quinidine not bound to protein varied from 16 8 to 23 4% Mean kinetic variables for total quinidine were volume of distribution 2 0 liters/Kg elimination half life 6 3 hours total clearance 3 8 ml /min /Kg These values are very similar to those reported previously in a study of a different group of subjects The elimination half life of unbound quinidine (5.2 hours) was similar to that of total quinidine although the difference did reach statistical significance However the apparent volume of distribution of the unbound drug (8 8 liters/Kg) and the total clearance of unbound drug (19.8 ml /min /Kg) are more than four times greater than corresponding values based on total quinidine concentrations The findings confirm those of a previous study [1] and clearly indicate that pharmacokinetic studies of quinidine based upon total rather than the pharmacologically active unbound fraction greatly underestimate the extent of distribution and the total metabolic clearance of the unbound drug However the half life of elimination of total and unbound quinidine are similar inasmuch as the extent of protein binding appears to be essentially independent of total concentration

Fig 5 shows representative serum concentration curves for total and unbound quinidine

Relation between pharmacokinetics and pharmacodynamics Table II shows correlation coefficients for total and unbound serum quinidine concentrations measured at the end of the infusion and at 0 25 hour intervals thereafter versus pharmacodynamic changes at the corresponding times expressed as increases over the pre infusion baseline values Very few of the correlations approached statistical significance Increases in heart rate were negatively correlated with total and unbound serum quinidine concentrations at all four points in time indicating that higher quinidine concentrations were not associated with greater increases in heart rate Similar negative associations were noted with changes in the corrected QT interval No consistent association was observed between serum quinidine concentrations and QRS duration V_{cf} or EF

Discussion

The effect of therapeutic doses of quinidine on the myocardial contractile state in vivo are incompletely understood We therefore evaluated the effects of a single intravenous dose of quinidine on left ventricular performance in healthy individuals utilizing echocardiography as a sensitive and reliable noninvasive method for assessment of drug induced changes in myocardial contractility

The injection of a single therapeutic intravenous dose of quinidine significantly increased ventricular rate and prolonged the corrected QT interval Effects lasted only for about 30 minutes after the end of the infusion following which these variables reverted toward pre quinidine baseline values Quinidine induced cardioacceleration observed in the present study was similar to that found in previous studies of intravenously administered quinidine lactate The effect of quinidine on heart rate depends upon the specific experimental preparation Reflex sympathetic stimulation may explain the acceleration of heart rate observed in intact conscious dogs given oral dihydroquinidine [1] The quinidine induced increase in heart rate was almost completely blocked by propranolol In humans however 160 mg of oral propranolol daily did not prevent the increase in heart rate after an acute intravenous dose of quinidine seen without propranolol In anesthetized open chest dogs a reduction of the heart rate after intravenous quinidine was observed [17] However anesthesia and thoracoto-

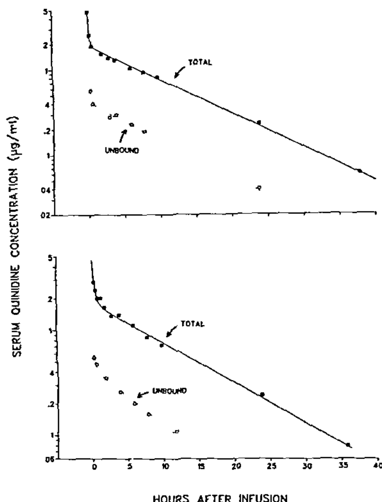


Fig 5 Serum concentrations of total and unbound quinidine in subjects W E (*above*) and D S (*below*) following intravenous quinidine infusion Also shown are pharmacokinetic functions determined by least squares regression analysis See Table I for pharmacokinetic variables

Table I Pharmacokinetics of total and unbound serum quinidine following a single intravenous dose

Subject	Age/Sex	Wt (Kg)	Mean (±SE) per cent unbound quinidine		Volume of distribution (liters/Kg)		Elimination half life (hours)		Total clearance (ml/min/Kg)	
					Total	Unbound	Total	Unbound	Total	Unbound
H O	33/M	70	19.7	(± 0.9)	2.52	11.94	6.66	6.03	4.37	22.88
W T	26/M	73	20.0	(± 0.9)	1.73	7.03	5.87	4.10	3.41	19.79
R S	24/F	52	22.4	(± 0.8)	1.65	7.25	4.75	4.13	4.01	20.20
D S	27/M	60	19.7	(± 0.4)	2.[illegible]	11.03	7.88	5.73	3.74	22.25
S M	27/M	70	18.7	(± 1.1)	1.53	6.40	4.99	3.54	3.55	20.89
P M	23/M	74	22.3	(± 0.6)	1.81	7.80	6.08	5.68	3.44	15.85
M H	22/F	52	20.9	(± 0.8)	2.27	9.49	6.24	5.21	4.19	21.05
R A	22/M	70	16.8	(± 0.3)	1.47	7.1[illegible]	5.98	4.39	2.85	18.88
N B	23/M	64	23.4	(± 0.9)	3.00	11.67	6.66	6.19	5.21	21.79
W E	23/M	80	20.5	(± 0.5)	1.84	8.54	7.52	6.86	2.83	14.38
Mean (± SE)					2.03 (± 0.16)	8.83 (± 0.65)	6.26 (± 0.31)	5.18 (± 0.34)	3.76 (± 0.23)	19.80 (± 0.87)

Table II Relation of total and unbound serum quinidine concentrations to cardiac effects

	Correlation coefficient of serum concentration versus				
Sampling time	*Increase in heart rate*	*Prolongation of QRS*	*Prolongation of QTc*	*Increase in V*	*Increase in EF*
End of infusion					
Total	−609 (p < 05)	−2?9	−.393	−251	+00?
Unbound	−605 (p < 05)	−.305	−.380	−308	−070
0.25 hr post infusion					
Total	−649 (p < 05)	+425	−569 (p < 10)	+338	+534
Unbound	−742 (p < 02)	+25?	−662 (p ≅ 05)	+413	+640 (p < 10)
0 5 hr post infusion					
Total	−616 (p < 03)	+010	−506 (p < 10)	−068	+15?
Unbound	−437	−145	−337	−222	−079
0 75 hr post infusion					
Total	−.512 (p < 1)	−138	−481 (p < 1)	+481	+4??
Unbound	−5?6 (p < 1)	−151	−471 (p < 1)	+460	+574 (p < 10)

Level of significance given in parentheses when the correlation approached significance
Expressed as increments over pre quinidine baseline value

my as such can profoundly influence hemodynamics and myocardial contractility making it difficult to interpret the effects of quinidine in this setting

Quinidine produced no significant changes in systolic or diastolic blood pressure in our study Ferrer and associates observed a fall in aortic blood pressure after a single oral dose of 0 8 g of quinidine sulfate in only about 50% of healthy subjects Quinidine induced hypotension seen under various experimental conditions has been attributed both to a central and peripheral effect of the drug but neither mechanism is well documented The increase in heart rate and EF after intravenous quinidine in our study could represent reflex changes that offset any hypotensive effect of the drug However James and Nadeau observed a slight increase in heart rate in anesthetized dogs when quinidine was injected through the sinus node artery suggesting a direct stimulatory effect of quinidine on the sinus node In any case a nontoxic intravenous dose of quinidine appears to have negligible hypotensive effects on resting healthy subjects These findings do not necessarily apply to patients with impaired myocardial function

Quinidine infusion caused a short acting but significant increase in V and EF Like other indices of cardiac contractility these parameters are influenced by pre and afterload as well as by heart rate Afterload as reflected by systolic and diastolic blood pressure did not increase and therefore probably does not account for the positive inotropic effect of quinidine Tachycardia however might have contributed to the improvement of contractility In addition the anticholinergic action of quinidine by moderating the influence of the vagus on the heart might also have contributed to enhancing V and EF In any case the findings indicate that a therapeutic dose of intravenous quinidine has no negative inotropic effects in healthy humans under the experimental conditions of this study

The kinetic behavior of intravenous quinidine administered as the gluconate salt is similar to that of quinidine given as the lactate Protein binding of quinidine also was similar to that reported previously Use of total rather than unbound serum quinidine concentrations leads to considerable underestimation of the extent of drug distribution and metabolic clearance since only the unbound fraction in serum is available for distribution and clearance

In contrast to a previous report total and unbound quinidine concentrations failed to correlate with acute ECG changes Edwards and colleagues demonstrated a weak correlation between quinidine plasma concentration and the QTc interval after a single oral dose A stronger association between quinidine concentration and cardiac effects might arise if achievement of equilibrium between serum and tissues were assured as would occur during multiple-dose therapy

Summary

Ten healthy volunteers received 300 mg of quinidine base as the gluconate salt by 15 minute intravenous infusion Physiologic variables moni tored before during and for 24 hours after the infusion were electrocardiogram systolic and diastolic blood pressure echocardiogram and carotid pulse tracing During quinidine infusion mean ventricular rate increased by 18% (67 1 to 79 5 beats per minute) and corrected QT interval increased by 54% (0 44 to 0 68 sec) QRS duration did not change significantly nor did systolic or diastolic blood pressure Ejection fraction (EF) measured by echocardiography did not decrease during quinidine infusion but rather increased by 12% (0 58 to 0 65) Mean rate of circumferential fiber shortening (V ,) likewise increased by 22% from 1 15 to 1 40 per second Over the 24 hours post infusion all monitored physiologic variables fluctuated considerably in the case of EF and V , apparently random variations over time were as great as those attributable to quinidine infu sion Mean (and range) kinetic variables for quin idine were volume of distribution 2 03 (1 47 to 3 00) liter/Kg elimination half life 6 3 (4 8 to 7 9) hours total clearance 3 8 (2 8 to 5 2) ml / min /Kg Neither total nor unbound serum quin idine concentrations were significantly correlated with physiologic changes Thus intravenous quinidine in the doses studied did not have nega tive inotropic effects in a series of healthy hu mans

Dr Och is supported by Grant Oc/3 from Deutsche Forschungsgemeinschaft Bonn Bad Godesberg Federal Republic of Germany Dr Greenblatt is supported in part by Grant MH 12?9 from the United States Public Health Service (USPHS) Dr Woo was the recipient of a research fellowship (HL-05723) from the USPHS This work was don in part during the tenure of the following research grant in aid awards (to Dr Greenblatt) No 13-056-?56 from the American Heart Association Western Massachusetts Division and the American Heart Association Massachusetts Affiliate Inc and No 13 51 ?6 from the American Heart Association Central Massachusetts Division We are grateful for the assistance of Ann Werner Kate Franke Lawrence J Moschit to Jerold S Harmatz and Dr Dean S MacLaughlin Dr MacLaughlin is supported by USPHS Grant GM 23430 to the Boston Collaborative Drug Surveillance Program

REFERENCES

1. West T H C and Amory D W Single fiber recording of the effects of quinidine at atrial and pacemaker sites in the isolated right atrium of the rabbit J Pharmacol Exp Ther 130 183 1960
2. Kennedy B L and West T L Factors influencing quinidine induced changes in excitability and contractility J Pharmacol Exp Ther 168 4? 1969
3. Tomoda H Chuck, L and Parmley W W Comparative myocardial depressant effects of lidocaine ajmalin propranolol and quinidine Jpn Circ J 36 433 1972
4. Hammermeister K E, Boerth R C and Warbasse J R The comparative inotropic effects of six clinically used antiarrhythmic agents AM HEART J 84 643 1972
5. Markiewicz W, Winkle R, Binetti G Kernoff R, and Harrison D C Normal myocardial contractile state in the presence of quinidine Circulation 53 101 19 6
6. Greenblatt D J Pfeifer H J Ochs H R Franke K MacLaughlin D S Smith T W and Koch Weser J Pharmacokinetics of quinidine in humans after intravenous intramuscular and oral administration J Pharmacol Exp Ther 202 365 19 ?
7. Ochs, H R Greenblatt D J Woo E Franke K, and Smith T W Effect of propranolol on pharmacokinetics and acute electrocardiographic effects following intravenous quinidine in humans Pharmacology 17 301 1978
8. Ochs, H R Greenblatt D J Woo E, and Smith T W Reduced quinidine clearance in elderly persons Am J Cardiol 42 481 1978
9. Conrad K A Molk B L and Chidsey C A Pharmacokinetic studies of quinidine in patients with arrhythmia Circulation 55 1 1977
10. Hirschfeld D S Ueda C T Rowland M, and Scheinmann M M Clinical and electrophysiological effects of intravenous quinidine in man Br Heart J 39 309 1976
11. Mason J W Winkle R A and Ingels N B Hemodynamic effects of intravenously administered quinidine on the transplanted human heart Am J Cardiol 40 99 1972
12. Woo E and Greenblatt D J Pharmacokinetic and clinical implications of quinidine protein binding J Pharm Sci 68 466 1979
13. Marquardt D W An algorithm for least quares esti mation of nonlinear parameters, J Soc Ind Appl Math 11 431 1963
14. Gibaldi, M and Perrier D Pharmacokinetics, New York 19 5 Marcel Dekker Inc
15. Greenblatt D J and Koch Weser J Clinical pharmacokinetics N Engl J Med 293 702 964 1975
16. Duchene Marullaz P, Delort P and Selecky F V Influence de la quinidine sur la frequence cardiaque du chien non narcose C R Soc Biol 163 1157 1969
17. Stern S Haemodynamic changes following separate and combined administration of beta blocking drugs and quinidine Eur J Clin Invest 1 423 1971
18. Vatner S F and Braunwald E Cardiovascular control mechanisms in the conscious state N Engl J Med 293 970 1975
19. Ferrer M I Harvey R M Werko L Dresdale D T, Cournand A, and Richards D W Some effects of quinidine sulfate on the heart and circulation in man AM HEART J 36 816 1949
20. James T N and Nadeau R A The mechanism of action of quinidine on the sinus node studied by direct perfusion through its artery AM HEART J 67 801 1964
21. Edwards, J R Hancock B W and Savnor R Correlation between plasma quinidine and cardiac effect Br J Clin Pharmacol 1 455 1974

Limitations of the standard transthoracic electrocardiogram in detecting subendocardial ischemia

R James Barnard Ph D
Gerald D Buckberg M D
Henry W Duncan M Sc
Los Angeles Calif

In a recent study we showed that a left ventricular *transmural ECG* recorded from leads implanted on endocardial and epicardial muscle provided a reliable and instantaneous guide to the adequacy of subendocardial perfusion [1] Under noninvasive clinical circumstances the presence of ischemia can be evaluated electrocardiographically only by use of the external *transthoracic* ECG where chest wall leads must be used

The present study was designed to compare the relative sensitivities of the transthoracic and transmural ECGs to detect myocardial ischemia We studied chronically instrumented dogs with patent coronary arteries Global left ventricular ischemia was produced by giving isoproterenol (Isuprel Winthrop Laboratories New York N Y) and segmental ischemia was produced with graded degrees of coronary occlusion in dogs who were made to exercise We measured regional myocardial blood flow while recording simultaneous transthoracic and transmural ECGs

Materials and methods

Experimental procedure Seven adult mongrel dogs weighing 21 to 26 kg were anesthetized with thiamylal sodium (Surital) 30 mg /kg and placed on a Bird respirator anesthesia was maintained with methoxyflurane (Metofane) Catheters were placed into the descending aorta and left atrium as described previously [1] Konigsberg pressure transducers (P 20) were placed in the descending aortic wall and Statham electromagnetic flow transducers and vascular occluders were placed around the circumflex coronary artery

A hook electrode similar to that described by Guyton was inserted through the left ventricular wall and attached to the endocardium in an area perfused by the left circumflex coronary artery A miniature electromyogram (EMG) electrode (Grass Instruments Inc) was attached to the epicardium which enabled us to record a left ventricular transmural ECG [1] All electrodes and catheters were tunneled subcutaneously to the back of the neck where they were exteriorized and protected by a jacket [3]

Measurements The Konigsberg transducers were calibrated against the aortic catheters and pressure recorded on a Honeywell 1858 Visicorder The pressure recordings were analyzed by planimetry to calculate myocardial oxygen demands from the tension time index (TTI) of Sarnoff and co workers and potential subendocardial blood supply from the diastolic pressure time index (DPTI) The ratio of these indices DPTI/TTI was used to assess the myocardial oxygen supply/demand balance as described previously [1, 3]

ECGs were recorded on a Visicorder using Sanborn ECG preamplifiers To record the external transthoracic ECG areas on the dorsal ventral and lateral aspects of the chest were shaved and standard plate electrodes attached to

From the D partm nt f Surg y and K n iol gy Uni ers ty of Californ a Los Ang les

Supported by Public Health Service (t HL 53 nd Bi medical Research Support Gra t R J B n (rt I I Public H alth Service Career De elopment Aw rd HL 00

Recei ed f r publ cati n Jan 1 1 3

Acc pted for publicati n M ch 1979

Reprint requests t R J mes Barn rd Ph D Dep t of Surg ry B 375 UCLA M dical Center Los Ang l s C lif

Table I Effect of isoproterenol and circumflex coronary artery occlusion on myocardial O_2 supply/demand indices

	Rest	Isoproterenol	Control exercise	Mod occlusion exercise	Severe occlusion exercise
HR (beats/min)	91 6 ± 6 1	206 1 ± 5 7	207 ? ± 10 7	216 4 ± 8 2	214 5 ± 7 0
DPTI (torr sec/min)	3 83 ± 137	/8/ ± 1?9	3 18? ± 257	3 104 ± 4 6	2 550 ± 161
TTI (torr sec/min)	1 513 ± 150	18 8 ± 158	3 510 ± 313	3 380 ± 305	3 302 ± ?03
DPTI/TTI	2 60 ± 0 02	0 41 ± 0 04	0 92 ± 0 06	0 91 ± 0 09	0 78 ± 0 07

Values are m n ± SE
I opr te enol signifi tly d fferent fr m re t ($p < 0.05$)
Occlusion significantly different f m control exercis ($p < 0.05$)

record directly across the chest in two directions The internal transmural ECG was recorded directly across the left ventricular wall

The total and regional coronary flows were measured by injecting batches (at least 3 million each) of 8 10 μ microspheres labeled with [14] Ce [8] Sr Sc and [1] I into the left atrium Arterial reference samples were withdrawn continually (15 ml /minute) for 120 seconds at rest and 90 seconds during exercise or isoproterenol infusion as described previously [5]

After completing the chronic experiments the dogs were anesthetized with Surital and killed by an intracardiac injection of potassium chloride Hearts were removed and placed in ice cold saline solution for 24 hours to facilitate subsequent sectioning The anterior and posterior left ventricular walls were cut into inner middle and outer myocardial layers of approximately equal thickness and analyzed for radioactivity in a Nuclear of Chicago pulse height analyzer Total and regional flows were calculated as described previously

Test procedures

Isoproterenol Isoproterenol a drug known to cause global subendocardial ischemia [8] was infused into seven dogs at doses ranging from 2 5 to 5 μg/kg minute Radioactive microspheres were injected before and after these infusion were given

Exercise Dogs were selected for the exercise series by ensuring that they would run on a treadmill before subjecting them to thoracotomy and chronic instrumentation The exercise studies were carried out 14 to 21 days after recovery from thoracotomy at a time when there was no clinical evidence of anemia fever or other sign of illness

The initiation of exercise testing consisted of running dogs on a treadmill at a work load and grade sufficient to produce a near maximum heart rate response During this steady state level of near maximum treadmill testing we recorded transmural and transthoracic ECGs mean and phasic coronary blood flow and intravascular pressures

Following this initial near maximum exercise test (usually on a different day) we ran dogs at work loads sufficient to raise heart rate to approximately 200 beats/minute We produced moderate coronary constriction during this steady state level of exercise by narrowing the circumflex coronary artery until mean coronary flow was reduced by approximately 30% We produced severe coronary constriction by narrowing the circumflex coronary artery further to reduce mean coronary blood flow during steady state exercise to approximately 55% below the level achieved during comparable work loads without coronary narrowing Each dog underwent at least one treadmill test where only moderate or severe coronary constriction was imposed Regional and phasic flow measurements and intravascular pressures were made when the coronary artery was either left open narrowed moderately or narrowed severely

Statistical analysis consisted either of t test or analysis of variance and the Scheffe test[1] $p \leq 0.05$ was used for statistical significance

Results

Isoproterenol Isoproterenol caused varying degrees of tachycardia and diastolic hypotension in all dogs and consequently produced a marked fall in the supply/demand ratio (DPTI/TTI) (Table I) Ischemic changes developed o transmural electrocardiogram in each of with unobstructed coronary ar r

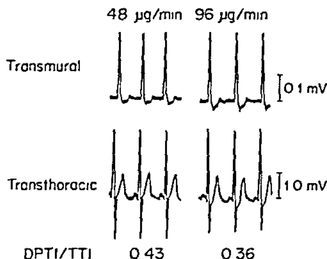


Fig 1 ECG responses to isoproterenol infusion

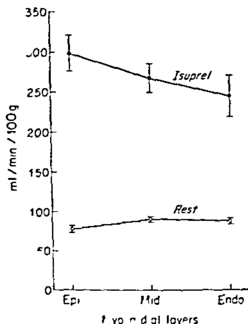


Fig 2 Effect of isoproterenol on left ventricular flow distribution.

DPTI/TTI was reduced below 0 5 by isoproterenol infusion (Fig 1) In contrast only slight J point depression or no ECG changes occurred during simultaneous recording of the transthoracic ECG in these dogs

The dosage required to produce the ischemic ECG changes varied in different dogs two developed ischemia at the lowest dose and three required higher doses DPTI TTI was highest (0 92 and 1 01) in two dog that did not develop ischemia despite a 5 µg kg minute isoproterenol infusion

During the test period coronary blood flow was

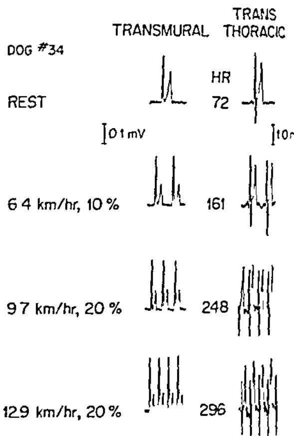


Fig 3 Transmural and transthoracic ECG responses during near maximum exercise test.

distributed preferentially toward the subendocardium endocardial/epicardial flow was 1 13 (Fig 2 Table II) Although left ventricular blood flow increased to all myocardial layers during the isoproterenol infusion which produced ischemia in the five dogs this flow became redistributed away from subendocardial muscle Subepicardial flow rose 288% while subendocardial flow rose by only 180% Consequently the endocardial/epicardial flow fell from 1 13 to 0 81 ($p < 0.05$) Flow distribution remained homogeneous (epicardial endocardial flows were 0 98 and 1 03) during the isoproterenol infusion in the two dogs which did not show ischemia on the transmural ECG

Exercise No ischemic changes developed in either the transmural or transthoracic ECG during the initial near maximum treadmill test (heart rate 267 ± 9 beats/minute) in seven dogs Despite the severe tachycardia the transmural ECG recordings showed a stable baseline and the recording fidelity was such that each record could be analyzed readily (Fig 3) In contrast two of seven standard external transthoracic ECGs

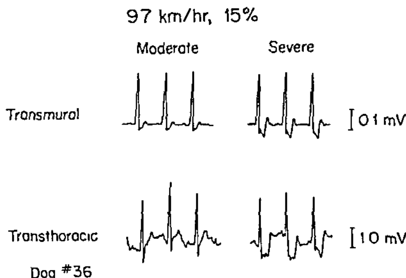


Fig 4 Transmural and transthoracic ECG responses to moderate and severe coronary occlusion

Table II Effect of isoproterenol and circumflex coronary artery occlusion on left ventricular blood flow

			Control exercise		*Mod occlusion exercise*		*Severe occlusion exercise*	
	Rest	*Isopro-terenol*	*LAD area*	*Circumflex area*	*LAD area*	*Circumflex area*	*LAD area*	*Circumflex area*
Mean flow (ml /100 gm min)	84 7 ±4 8	269 8 ±26 3	271 7 ±28 0	278 6 ±42 0	308.5 ±33.9	198 9* ±17 1	316 3* ±33 5	1 6.8 ±17 8
Endo/epi flow	1 13	0 81	0 99	1 05	1 06	0 43	0 98	0 48*

Values are means ± S E
Isoproterenol significantly different from rest ($p < 0.05$)
*Occlusion significantly different from control exercise ($p < 0.05$)

could not be interpreted during maximum treadmill testing because of motion artifact

During treadmill testing moderate coronary narrowing (29% reduction in exercise flow) produced ischemia which was evident in the transmural ECG in each of the seven dogs The simultaneously recorded standard external electrocardiogram however showed either no change or only slight J point depression at this time It was only with severe coronary narrowing (sufficient to reduce exercising coronary flow to 55% below control levels) that we could produce ST depression on the external transthoracic ECG (Fig 4) Such narrowing caused alarming changes in the transmural ECG and resulted in ventricular fibrillation in one dog (Fig 5)

Transmural and regional flow to the anterior myocardium supplied by the unobstructed left anterior descending coronary artery remained relatively constant (271 ± 27 309 ± 34 and 316 ± 34 ml /100 gm minute) during the steady state level of activity while the circumflex coronary artery was opened or moderately or severely narrowed

Moderate narrowing of the circumflex coronary artery decreased mean transmural flow in the area supplied by that artery from 287 6 ± 42 0 to 198 9 ± 17 ml /100 gm minute Epicardial muscle flow was however maintained at prestenotic levels while flow to the midmyocardial and subendocardial muscle layers was reduced significantly (Fig 6 Table II) Subepicardial muscle blood flow could not however be maintained when the circumflex coronary artery was narrowed severely enough to reduce mean coronary flow to 126 8 ± 17 8 ml /100 gm minute (55% below control values) subepicardial flow fell from 261 1 ± 38 2 to 166 5 ± 25 6 ml /100

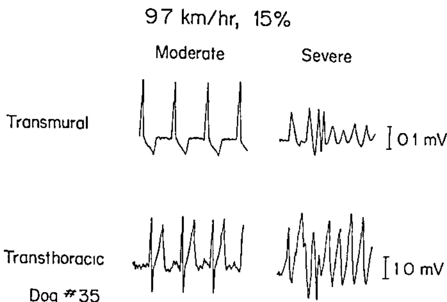
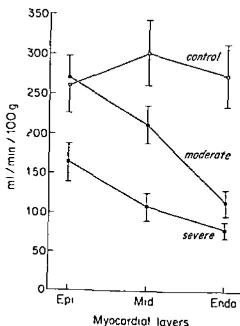


Fig 5 Transmural and transthoracic ECG responses to moderate and severe coronary occlusion



6 Coronary blood flow response to moderate and severe …umflex occlusion during exercise

minute while subendocardial flow was …uced further to 79 7 ± 11 8 ml /100 gm min … (Fig 6)

…cussion

…he extreme vulnerability of left ventricular …endocardial muscle to ischemia is emphasized … reports showing that most myocardial infarc…ns in patients with coronary artery disease are …ier limited to or most severe in the left ventric…ular inner shell Recent studies in dogs wit… graded coronary stenoses show that moderat… coronary narrowing restricts subendocardial flow preferentially with subepicardial flow remainin… normal Subendocardial underperfusion was als… always most severe with coronary narrowing that reduced flow transmurally[1, 12] Our data are consistent with the above findings and show that the standard transthoracic ECG recorded from chest wall leads is relatively insensitive to moderate subendocardial underperfusion transmural hypoperfusion is necessary in order to be detected by the monitoring technique which is used most often in clinical practice

We used isoproterenol a drug known to produce subendocardial ischemia and necrosis[7] to test the transmural lead system since our previous studies have demonstrated that with isoproterenol coronary flow is redistributed away from the subendocardial muscle Although isoproterenol caused a marked augmentation in total left ventricular flow (84 7 ± 4 8 to 269 8 ± 26 3 ml /100 gm minute) subepicardial flow rose by 288% while subendocardial flow rose by only 180% resulting in an endocardial/epicardial flow of 0 81 Ischemia became evident on the transmural ECG but the simultaneously recorded transthoracic ECG remained normal As with our previous reports the supply/demand ratio (DPTI/TTI) was useful in predicting the ischemia produced by isoproterenol[1, 7] Prominent ST depression was seen in the transmural ECG in

each of five dogs when this ratio was < 0 5 and did not develop in two other dogs (receiving comparable isoproterenol infusions) with DPTI/TTI > 0 50 This ratio however is useful only when the coronary arteries are unobstructed since the diastolic blood pressure is always reduced beyond any flow limiting coronary stenosis especially when coronary blood flow is increased as with exercise[13,14] Consequently ischemia would be expected to develop at a much higher DPTI/TTI when coronary stenosis is present

It is not surprising therefore that ischemia became evident on the transmural ECG during treadmill testing in all dogs with coronary stenosis even though DPTI/TTI was always > 0 50 (0 91 ± 0 09 with moderate stenosis and 0 78 ± 0 07 with severe stenosis) As with the ischemia produced by isoproterenol the transthoracic ECG remained normal during exercise with moderate coronary stenosis and preferential subendocardial underperfusion and changed only when we made the stenosis more severe and caused transmural hypoperfusion The most pronounced redistribution of coronary blood flow away from the subendocardium (endocardial/epicardial flow falling from 1 05 to 0 43) occurred with coronary narrowing sufficient to reduce exercising coronary blood flow only 29% below levels achieved during exercise with patent coronary arteries This marked redistribution of flow occurred because subepicardial vessels were able to dilate sufficiently to maintain coronary blood flow at prestenotic levels while endocardial flow fell 57%

Since the early work of Hellerstein and Katz and Wolferth and co workers ST depression has been the hallmark of ischemia which is presumed to be limited to the subendocardial region Our studies provide evidence that while the subendocardial muscle is indeed ischemic when the transthoracic ECG shows ST changes this ischemia is transmural rather than confined to the inner shell Our combined use of the transmural ECG and direct blood flow measurements (microspheres) show that the transthoracic ECG is of limited value in detecting early subendocardial relative underperfusion

Biochemical support of our conclusions about the limitations of transthoracic ECGs can be marshalled from the studies of Case and co workers and Scheuer and Brachfeld[1] who reported coronary sinus lactate and potassium increases during graded coronary occlusion that precede the ischemic ST setment changes seen on the external transthoracic ECG The need to be suspicious of the limitations of noninvasive clinically available techniques in detecting subendocardial ischemia has been emphasized by others[23] Studies by Sayen and associates showed that even myocardial surface electrocardiography had limited sensitivity in detecting subendocardial ischemia They observed marked ST segment changes on an intramural ECG with severe reductions of subendocardial tissue P_o and contractility before epicardial leads detected the ischemia

We realize that a multiple chest lead system may be 10% to 20% more sensitive in detecting ischemia than one or two transthoracic lead systems which are often used clinically and which we used in our dogs[2] We realize also that exercise electrocardiography is less sensitive for single than double or triple vessel disease However we do not feel that these factors can explain the lack of our ability to use the standard transthoracic ECG to detect ischemia which is limited to the subendocardium Isoproterenol produced global subendocardial ischemia[7] while the transthoracic ECG did not change appreciably

The results of our study have potential clinical implications in that our documentation of limitation of the transthoracic external ECG clarifies why some patients who complain of angina during treadmill testing do not show ischemic ECGs when chest leads are monitored The occurrence of subendocardial ischemia before ST depression is seen on the external ECG together with the need for transmural ischemia to be present before this lead system is sensitive suggests that extreme caution must be practiced when patients are made to exercise for prolonged periods at work loads which elicit signs of ST depression on the external ECG

REFERENCES

1 Barnard R J Duncan H W Livesay J J, and Buckberg G D Coronary vasodilator reserve and flow distribution during near maximal exercise in dog J Appl Physiol 43 988 1977

2. Guyton, R A Subendocardial S T segment changes during acute coronary occlusion Ann Thoracic Surg 20 5? 19 5

3. Foss M L and Barnard R J A vest to protect exposed

chronic implants in dogs Lab Animal Care 19 113 1969

4 Sarnoff S J Braunwald E Welch G H Jr Case R B Stainsby W N and Marcs R Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension time index Am J Physiol 192 148 1958

5 Buckberg G D Fixler D E Archie J P and Hoffman J I E Experimental subendocardial ischemia in dogs with normal coronary arteries Circ Res 30 67 1972

6 Buckberg G D Luck J C Payne D G., Hoffman J I E Archie J P and Fixler D E Some sources of error in measuring regional blood flow with radioactive microspheres J Appl Physiol 31 598 1971

7 Buckberg G D and Ross G Effects of isoprenaline on coronary blood flow Its distribution and myocardial performance Cardiovasc Res 7 492 1973

8 Handforth C P Isoproterenol induced myocardial infarction in animals Arch Pathol. 73 161 1962

9 Winsor T Mill. B Winburg M W Howe B B and Berger H J Intramyocardial diversion of coronary blood flow Effects of isoproterenol induced myocardial ischemia Microvasc Res 9 261 1975

10 Ferguson G A Statistical Analysis in Psychology and Education New York 1971 McGraw Hill Book Co p 270

11 Ball R M and Bache R J Distribution of myocardial blood flow in the exercising dog with restricted coronary artery inflow Circ Res 38 60 1976

12 Bagger H Regional blood flow in the left ventricular wall of dogs with a graded coronary artery stenosis Acta Physiol Scand 100 154 1977

13 Gould L K Lipscomb K and Calbert C Compensatory changes of the distal coronary vascular bed during progressive coronary constriction Circulation 51 1085 1975

14 Gould L K Pressure flow characteristics of coronary stenosis in unsedated dogs at rest and during coronary vasodilation Circ Res 43 242 1978

15 Hellerstein H K and Katz L N The electrical effects of injury at various myocardial locations Am Heart J 36 184 1948

16 Wolferth C C Bellet S Livezey M M and Murphy F D Negative displacement of the RS T segment in the electrocardiogram and its relationships to positive displacement An experimental study Am Heart J 29 220 1945

17 Case R B Nasser N G and Crampton R Biochemical aspects of early myocardial ischemia An Cardiol 24 766 1969

18 Scheuer J and Brachfeld N Coronary insufficie Relations between hemodynamic electrical and chemical parameters Circ Res 18 178 1966

19 Guyton R A., McClenathan J G Newman C E Michaelis L L Significance of subendocardial segment elevation caused by coronary stenosis in the Am J Cardiol 40 373 1977

20 Sayen J J Sheldon W F Peirce G and Kuo P Polarographic oxygen the epicardial electrocardiogr and muscle contraction in experimental acute regio ischemia of the left ventricle Circ Res 6 79 1958

21 Sayen J J Peirce G Katcher A H and Sheld W F Correlation of intramyocardial electrocar grams with polarographic oxygen and contractility in nonischemic and regionally ischemic left ventricle

22 Sayen J J Sheldon W F Peirce G Katcher A and Kuo P T Electrocardiogram myocardial oxy and contractility in scar and collaterally supplied mus after experimental coronary ligation Circ Res 11 1962

23 Vincent G M Abildskov J A and Burgess M Mechanisms of ischemic ST segment displaceme Evaluation by direct current recordings Circulati 56 559 1977

24 Chaitman B R Bourassa M G Wagniart P Corba F and Ferguson R J Improved efficiency of treadm exercise testing using multiple lead ECG system basic hemodynamic exercise response Circulation 57 1978

25 Mason R E Likar I Biern R O and Ross R Multiple lead exercise electrocardiography Experien in 107 normal subjects and 67 patients with an pectoris and comparison with coronary cineartenog phy in 84 patients Circulation 36 517 1967

26 McHenry P L Phillips J F and Knoebel S Correlation of computer quantitated treadmill exer electrocardiogram with arteriographic location of co nary artery disease Am J Cardiol 30 747 19

27 Kaplan M A Harris C N Aronow W S Park D P and Ellestad M H Inability of the submaxim treadmill stress to predict the location of corona disease Circulation 47 250 1973

Sialic acid–depleted red cells following acute myocardial infarction

Victor A Hanson Jr M D
Stephen A Landaw M D Ph D
Michael Flashner Ph D
Stennis D Wax M D
Watts R Webb M D
Syracuse N Y

Sialic acid (SA) is the terminal moiety of a membrane glycoprotein and is responsible for the negative surface charge on the red blood cell (RBC) Chien and others have reported decreased red cell SA in a patient with a stroke while Resnitzky and others[1] have demonstrated a reduction in red cell electrophoretic mobility (EM) a measure of surface charge in patients with acute myocardial infarction and venous thrombosis of the lower extremities Because these observations suggest that a relationship between chemical changes on the red cell and disturbances of intravascular hemostasis may exist erythrocyte SA in patients following acute myocardial infarction was measured and the hemodynamic effects of SA depleted red cells in an animal model were studied

Materials and methods

Patients Within 48 hours of hospital admission blood samples were collected in heparinized tubes by venipuncture from patients with acute myocardial infarction

Following centrifugation of 4 ml of collected human blood at 3 800 rpm for 18 to 20 minutes at room temperature the plasma and buffy coat were discarded The red cells were washed three times in 0 9% saline solution and 9 volumes of fresh 0 9% saline solution was added to make a 1 10 erythrocyte saline suspension SA was extracted from the washed erythrocyte suspension by adding 3 ml 0 4N H_2SO_4 to the erythrocyte suspension placed in a water bath at 80° C for 1 hour To each tube 0 6 ml 15% K Fe (CN) 3H O followed by 0 6 ml 30% Zn ($C_2H_3O_2$) were added This was then centrifuged at 2 400 rpm for 5 minutes The clear supernatant was removed and the SA content was measured by the thiobarbituric acid assay described by Warren and expressed in micromoles per 0 1 ml RBCs

SA reference values were obtained from a control group of healthy men and women 22 to 45 years of age The diagnosis of myocardial infarction was established by clinical impression electrocardiograms and enzyme determinations

Animals Seven mongrel dogs (10 to 12 kg) were anesthetized with intravenous sodium pentobarbital (30 mg/kg) intubated and placed on a volume respirator delivering room air and mean femoral artery pressure Heart rates were continuously monitored on an oscilloscope and intermittently recorded The pulmonary microcirculation was filmed according to the technique described by Wax The widths of typical alveolar capillary beds were measured in microns and changes were expressed as a percentage of control values After obtaining control hemodynamic measurements and blood samples for control determinations of red cell SA and EM five

From the D partments of Surg ry nd Medici Veterans Administra ti n Med al C nter Upst t Medical C nter d Stat U ersity of N w Y k Coll ge f En ir m nt l Scie ce nd Forestry Syr se N Y

Rece ed f publi t on Jan 31 19 9
A cepted f p bl t n M rch 6 19 9

R print requests D Vict r A H nson Jr Vet ns Administrati n H sp t l Irv g A d Uni ers ty PL Syracuse N Y 13210

0002-8 03/80/040483 + 04$00 40/0 © 1980 The C V Mosby Co

Table I Dog red cell SA and EM after neuraminidase and storage

	SA (μmol/0.1 ml RBC)	EM (μ/sec/volt/cm at 25° C)
Reference value	0.043 ± 0.002 (SEM)	1.98 ± 0.07
Neuraminidase	0.028 ± 0.003 (p < 0.001)	1.5 ± 0.08 (p < 0.001)
Reference value	0.041 ± 0.002	2.02 ± 0.01
Stored blood (in vitro)	0.024 ± 0.003 (p < 0.001)	1.87 ± 0.02 (p < 0.001)

SEM = standard error of mean

animals were given intravenous *Vibrio cholerae* neuraminidase (VCN),* 875 units/kg, free of proteolytic activity and lecithinase at pH 5 while two animals were given the same dosage of boiled VCN[6] Serial measurements of red cell SA and EM were made and films of alveolar capillary blood flow were taken every half hour Mean femoral artery pressures and heart rates were intermittently recorded

Six other dogs were prepared like the first group and, in addition a Carolina flow probe was put around the pulmonary artery and a Swan Ganz catheter positioned in the right heart outflow tract so that measurements could be made of cardiac output pulmonary artery and pulmonary capillary wedge pressures This group was given VCN intravenously (875 units/kg) and subsequent changes in red cell SA and EM were measured and hemodynamic variations recorded

From each of nine splenectromized dogs 500 ml of whole blood was drawn under sterile conditions and stored in acid citrate dextrose (ACD) solution at 4° C 6 units for 28 days and 3 units for 48 hours Three dogs were autotransfused through in line filters with 28 day old blood and films of the pulmonary microcirculation were taken intermittently Three other dogs were given 28 day old blood with hemodynamic measurements recorded and three dogs were autotransfused with 48 hour old blood as a control

The determination of EM is based upon the relationship between the rate of movement of a particle in an electric field and the magnitude of its surface potential as described by Helmholtz and Smoluchowski[7] Dog blood collected [in] heparinized tubes from a Silastic catheter in [the] femoral vein was centrifuged at 2400 rpm [the] buffy coat and plasma discarded and the red cel[ls] washed three times in 0.9% saline solution a[nd] suspended in a sorbitol solution with an adjust[ed] pH of 7.4 (sodium bicarbonate buffer) and [an] ionic strength of 0.01 The sorbitol erythrocy[te] suspension was placed in the cell of the Ze[ta] meter* where EM was determined and express[ed] in microns per second per volt per centimet[er] corrected for temperature at 25° C

The statistical analysis of data was done on [a] Hewlett Packard calculator 9810A programm[ed] for the paired t test

Results

The mean erythrocyte SA value in 26 patie[nts] following acute myocardial infarction w[as] 0.021 ± 0.001 (SEM) μmol/0.1 ml RBCs com[pared] with a reference value of 0.031 ± 0.00[...] (p < 0.01)

In five dogs mean erythrocyte SA decrea[sed] from 0.043 ± 0.002 to 0.028 ± 0.003 (p < 0.00[1]) and mean EM decreased from 1.98 ± 0.07 μ/sec/volt/cm at 25° C to 1.5 ± 0.08 (p < 0.00[1]) after neuraminidase Mean cardiac index de[creased] from 2.3 ± 0.22 to 1.3 ± 0.16 (p < 0.0[...]) and the mean widths of typical alveolar capilla[ry] beds decreased 42.6% ± 0.5% (p < 0.01) In thr[ee] dogs following autotransfusion of 500 ml of [28] day old blood with a mean erythrocyte SA [of] 0.024 ± 0.003 and mean EM of 1.87 ± 0.02 th[e] mean cardiac index decreased from 2.0 ± 0.21 [to] 1.5 ± 0.21 (p < 0.2) and the mean widths [of] alveolar capillary beds decreased by 21.7% ± 0.9[%] (p < 0.01)

No significant changes in SA EM cardi[ac] index or alveolar capillary beds were seen follow[ing] injection of boiled neuraminidase

Discussion

In the patients studied with acute myocardi[al] infarction red cell SA was reduced by about o[ne] third while in the dog a one third or mor[e] reduction of red cell SA produced by the intrav[e]nous injection of neuraminidase and autotransfu[sion] of 28 day old blood resulted in myocardi[al] depression and decreased alveolar capillary blo[od] flow (Tables I and II) By causing perfusio[n]

*Grand Island Biological Co Grand Island N Y

*Zeta Meter Inc New York N Y

Table II Hemodynamics after neuraminidase and stored blood

	Cardiac index (L /min /m)	*Mean femoral artery pressure mm. Hg*	*Mean heart rate (beats/min)*	*Mean pulmonary artery pressure (mm Hg)*	*Mean pulmonary capillary wedge pressure (mm Hg)*
Control	2.3 ± 0.22 (SEM)	111	129	15	—
Neuraminidase	1.3 ± 0.16 (p < 0.01)	70	118	11	—
Control	2.0 ± 0.21	133	133	15	3.7
Stored blood (4 weeks)	1.5 ± 0.21 (p < 0.2)	130	130	20	5.5
Control	2.0 ± 0.21	133	153	—	—
Fresh blood	3.2 ± 0.31 (p < 0.1)	159	184	—	—

SEM = standard error of mean.

defects in the heart and lungs red cell clumping (created by a reduction of repulsive electrostatic forces and clearly seen in the films of the pulmonary microcirculation) may be the mechanism responsible for these hemodynamic changes

Although the percentage reduction in cardiac index and pulmonary flow patterns was similar the hemodynamic changes following neuraminidase were greater than those following stored blood (Table II) This difference is due to a greater concentration of SA depleted red cells produced by neuraminidase which caused no effects when boiled and injected intravenously

While the decrease in SA after neuraminidase and storage was in a similar range (35% and 44% respectively) the decrease in electrophoretic mobility after neuraminidase was 24% compared with 7% after storage (Table I) However the addition of calcium chloride to the stored blood before EM determinations all but eliminated this difference suggesting that citrate may increase the negative charge on the red cell by binding cations

The stability of the glycosidic linkage between SA and the rest of the glycoprotein makes enzymatic disruption a likely mechanism for the reduction of red cell SA following acute myocardial infarction although the source of the enzyme is unknown

If the same relationship between red cell SA senescence and the reticuloendothelial system described by Landaw[8] in the mouse exists in the human then the effects of SA depleted red cells should last about as long as it takes to clear them from the general circulation

Summary

A reduction of red cell SA in patients following acute myocardial infarction is reported and the effects of SA depleted red cells on cardiac index and alveolar capillary blood flow in the dog are described The mean red cell SA in 26 patients following acute myocardial infarction was 0.021 ± 0.001 compared with a mean of 0.031 ± 0.002 μmol /0.1 ml RBC in 12 normal subjects (p < 0.01)

In five dogs injected with neuraminidase an enzyme which removes SA from the red cell membrane a 43% decrease in mean cardiac index from 2.3 ± 0.22 to 1.3 ± 0.16 (p < 0.01) occurred In films of the pulmonary microcirculation the mean widths of typical alveolar capillary beds decreased 42.6% ± 5% (p < 0.01) In three other dogs, autotransfusion with SA-depleted stored blood resulted in a 25% decrease in mean cardiac index from 2.0 ± 0.21 to 1.5 ± 0.21 (p < 0.2) and a 21.7% ± 0.9% (p < 0.01) decrease in mean widths of typical alveolar capillary beds We conclude that a reduction of red cell SA follows acute myocardial infarction and that SA depleted red cells decrease cardiac index and alveolar capillary blood flow in the dog

The authors wish to thank Susan Naum Bedigian and Douglas Laughton for their valuable laboratory assistance and Kay Basile for the preparation of this manuscript

REFERENCES

1. Eylar E. Madoff M Brody O and Oncley J The contribution of sialic acid to surface charge of the erythrocyte J Biol. Chem. 237 1992, 1962.
2. Chien, S Cooper G Jan, K., Miller L., Howe C.,

Usami, S and Lalezari P N acetylneuraminic acid deficiency in erythrocyte membranes Biophysical and biochemical correlates Blood 43 445 1974
3 Resnitzky P Yaari A and Danon D Biophysical characteristics of erythrocytes during acute myocardial infarction and venous thrombosis Thromb Diathes Haemorrh 28 524 1972
4 Warren L The thiobarbituric acid assay of sialic acid J Biol Chem 234 1971 1959
5 Wax S D Pulmonary microcirculation J Surg 21 1970
6 Gottschalk A Glycoproteins London 19 2, Else Co p 381
7 Riddick T M Control of Colloid Stability Thro Zeta Potential Wynnewood Pa 1968 Livingston p 320
8 Landaw S Biological aspects of senescence in red ce J Lab Clin Med 89 581 1977

The abnormal heart rate response to a deep breath in borderline labile hypertension a sign of autonomic nervous system dysfunction

Louis C Johnston M D
Chicago Ill

Patients in this gray zone area of essential hypertension with somewhat elevated casual blood pressure levels on one visit but normal on another constitute a very common disorder in this country comprising about 10% of adults but perhaps twice that prevalence among university age students In describing patients in this marginal pressure zone some prefer the term labile hypertension which assumes that some pressures are occasionally normal and hypertensive target organ damage is absent[1, 3] Others prefer the term borderline hypertension appropriately noting that a few readings with a span of only several mm Hg on either side of some critical point e g 140/90 mm Hg is a highly artificial and certainly objectionable way to define a distinct nosologic labile category[2] This present study escapes that criticism however because the patients reported here demonstrated a marked pressure span one easily accepted as labile but too excessive to be considered merely borderline They are therefore henceforth referred to in this study as having labile hypertension (LHT)

The problem at once confronting the clinician is how seriously to view these occasional blood pressure elevations as most such persons do not become hypertensive patients only 12% of young airmen with labile readings advanced to sustained hypertension over a 20 year interval slightly higher as well as somewhat lower rates have been noted also over other similar extended periods[1, 2] However the vast majority of such persons commonly younger people are not destined to become permanent hypertensives and the early institution of chronic perhaps even life long drug therapy would appear a therapeutic adventure of dubious value and entailing certain drug risks Perhaps such youngsters are best considered as normal persons with an orienting or defense reflex somewhat more lively than most[3, 5]

That such transient elevations cannot be cavalierly disregarded however is dramatically shown by their increased incidence of vascular complications an over all reduction in life expectancy and the occasional development of sustained hypertension[1] [6] Over a 50 month period for example a slowly changing hemodynamic pattern has been observed in a minority of LHT patients to one of lower cardiac output lower heart rate and increased peripheral resistance the standard pattern of sustained essential hypertension [8] While such a course can occur the problem is selection of that unfortunate minority from the preponderant majority of healthy but similarly labile normal individuals not so destined to later become ill hypertensive patients A current capability of such a clinical distinction is not available and further research on the earlier phases of hypertension is sorely needed

A distinct deficit of autonomic neural control of the heart in labile or borderline hypertension was demonstrated in 1971 by Julius Pascual and London[9] who clearly showed in these patients a subnormal rise in the heart rate with full atropinization following complete beta adrer
ade Their important conclusion that

F om th Department of Card logv Grant Hosp tal of Chi go Ch cag Ill

Recei ed for publ cation Jan 31 19 9

Accepted for publicat n Sept 24 1979

Reprint request Louis C J hnston M D Grant H pital of Chicag 550 W Webste A e Chicag Ill 60614

000 8 03/80/04048 + 0 $00 70/0 © 1980 The C V Mosby Co

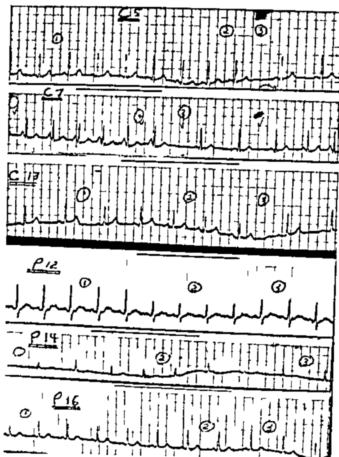


Fig 1 Three illustrative controls (C) *above* and three labile hypertensive patients (I) *below* The numbers with C and I refer to the subject designation in Table II The encircled numbers 1 2 and 3 refer to heart rate intervals at rest inspiration and expiration The horizontal bar above each strip marks the deep inspiration

onstrated a deficit of parasympathetic inhibition is supported by the work reported here Whether such a deficit is predictive of subsequent sustained hypertensive disease can be established only by long term prospective study

Methods

All patients meeting the prescribed blood pressure criteria were recruited consecutively and prospectively from the Hypertension Clinic of Grant Hospital and from the consulting practice of the author Their clinical characteristics are depicted in Table I To be eligible the blood pressure had to be less than 150/100 mm Hg supine at the time of the inhalation test and after a short period of supine rest (5 to 10 minutes) all but two had systolic pressures of 135 mm Hg or less and all but four had diastolic pressures of 80 mm Hg or less Also at any visit during the preceding 30 months two resting blood pressure

Table I Clinical characteristics of subjects

	Controls	Patients
Male/Female	13/3	5 11
Age (years)	40 ± 1?	4 1?
Height (cm)	170 ± 6	16? ± ?
Weight (kg)	77 ± 10	?1 ± 10
Blood pressure (mm Hg)		
At time of test		
Systolic	117 ± 8	131 6
Diastolic	73 ± ?	80 9
Maximum in 30 months		
Systolic	–	171 ± 11
Diastolic	–	10? 9

± 1 standard deviation

values while or while not on therapy had to be greater than 150/100 mm Hg and the systolic pressure had to be at least 25 mm Hg greater than at the time of the inhalation test The span of one patient was less 148/80 mm Hg on the test day and a maximum earlier value of 160/100 mm Hg Eight patients exhibited systolic rises on other visits of at least 40 mm Hg greater than on the test day reaching levels of 180/90 mm Hg or greater Two alcoholics and two distance runners had to be excluded (see below) All patients were ambulatory active and felt well None had or had ever had, proteinuria azotemia hemorrhagic or exudative retinopathy roentgenographic cardiomegaly, ventricular hypertrophy by electrocardiography, congestive heart failure or vascular ischemic disease of heart or brain All were clinically diagnosed as having borderline labile essential hypertension and none had received drug therapy or contraceptive steroids for at least one month preceding the test

The normal controls were similarly consecutively recruited from a group of healthy subjects undergoing routine outpatient periodic physical examination All exhibited resting supine pressures of 140/100 mm Hg or less all but two had pressures of 120/70 mm Hg or less The only exclusions were four alcoholics and two distance runners This exclusion was necessitated by the fixed heart rate response of the alcoholics to the inhalation test maneuver and the exaggerated response of the runners These individuals are currently under separate study

The body weight of the two groups was comparable While the average weight and height of the control group were slightly more than those of the patient group 77 kilograms and 170 cm

Table II Pulse rate response from rest to maximal inspiration and expiration (beats/minute b/m and percent change % Δ)

	Normal controls						Labile hypertension patients					
	1 Rest b/m	2 Inspiration b/m	2 Inspiration % Δ	3 Expiration b/m	3 Expiration % Δ	3 Expiration % Δ	4 Rest b/m	5 Inspiration b/m	5 Inspiration % Δ	6 Expiration b/m	6 Expiration % Δ	6 Expiration % Δ
		a	b†	a	b†	c†		a	b†	a	b†	c†
1	66	86	30	57	14	34	81	84	4	81	0	4
2	68	81	19	55	19	32	94	97	3	94	0	3
3	63	70	11	56	11	20	57	64	12	54	5	16
4	59	77	31	43	27	44	94	100	6	100	−6	0
5	86	97	13	59	31	39	86	91	6	75	13	18
6	61	75	23	55	9	27	103	111	8	100	3	10
7	91	97	6	57	37	41	81	86	6	75	7	13
8	63	77	22	57	10	26	64	73	14	61	5	16
9	68	81	19	63	7	22	86	86	0	75	13	13
10	51	60	18	50	2	17	77	84	9	73	5	13
11	65	84	29	47	28	44	75	88	17	70	7	20
12	54	68	26	46	15	32	94	97	3	94	0	3
13	65	81	25	56	14	31	79	88	11	73	8	17
14	58	75	29	50	14	33	64	81	38	63	2	2[illegible]
15	81	97	20	70	14	28	86	94	9	88	−2	6
16	51	70	37	48	6	31	84	84	0	81	4	4
Means	66	80	22	54	17	31	82	88	9	79	4	11

Significance of difference from normal controls"
Significance of differences from previous state 1 to 2a 1 to 3a 2a to 3a
4 to 5a and 4 to 6a not significant 5a to 6a

= < 0.0'5 = < 0.005 = < 0.0005

†2b $= \frac{2a-1}{1} \times 100$ 3b $= \frac{1-3a}{1} \times 100$ 3c $= \frac{2a-3a}{2a} \times 100$ 5b $= \frac{5-4}{4} \times 100$ 6b $= \frac{4-6a}{4} \times 100$ 6c $= \frac{5a-6}{5a} \times 100$

versus 71 kilograms and 165 cm only three controls and three patients exceeded an ideal weight range by more than 10 kilograms A single subject was underweight a patient weighing 52 kilograms and 170 cm tall The slight age discrepancy between patients and controls is considered below (see Discussion)

All controls but one were Caucasian as were all patients but one

While still supine and after the blood pressure had been recorded subjects were simply asked to inhale as deeply as possible but without gasping and then to comfortably exhale without pausing to a resting position while the heart rate was monitored by electrocardiography with a standard paper speed of 25 mm per second and a horizontal marker delineating by gross observation of the subject the visible inspiratory effort (see Fig 1) Intervals were measured from the peaks of the R waves The test was performed

B ild nd Blood Pressure Study Metropolitan Life Insurance Co Society f A tuaries, 1959

three times at approximately 30 second intervals and the complex with the longest expiratory pause (slowest expiratory heart rate) was used for statistical analysis of the control inspiratory and expiratory intervals The inspiratory interval selected was the shortest one during inspiration The expiratory interval used was the longest of the three intervals immediately following termination of the deep inspiration The control interval used was the average by visual inspection of the four intervals immediately preceding the inspiratory effort Performance of this maneuver in the standing position did not increase test sensitivity i e expiratory slowing of pulse rate was less not more in the standing position The deep breath maneuver in normal supine subjects greatly exaggerated the heart rate response over that noted during mere resting ventilation from one of a magnitude scarcely detectable on gross ECG inspection to those conspicuous mean responses of +22% inspiration and −17% expiration listed in Table II Resting ventilation heart

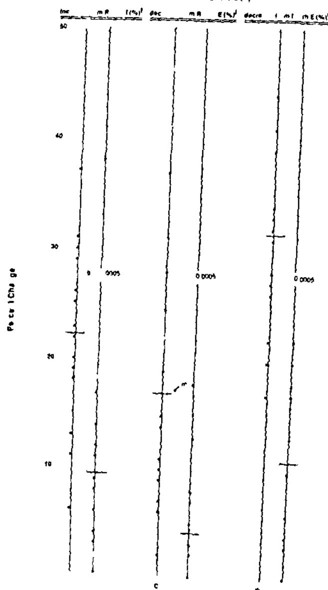


Fig 2 A comparison of percent change of pulse rate response ( ) of normal controls *(C)* and patients with labile hyperten sion *(P)* to a deep in piration *(I)* compared to rest *(R)* left pair to expiration *(E)* ompared to rest middle pair to expiration compared to in piration right pair For method of calculation of these ratios see leg nd to Table II

rate responsiveness in these normal subjects was limited to approximately 4' as has been well established[1] LHT patients showed minimal re sponsiveness to either normal resting ventilation or a deep breath

The significance of differences between mean values within each group and also between con trols and patients wa assessed respectively by paired and unpaired Student s t test

Results

The very highly significant differences in heart rate response between normals and LHT to a deep breath are shown in Fig 2 These differences and also the change within each group normal or LHT resulting from moving from res t inspiration to expiration are stated in Table II Several illustrative examples are shown in Fig I

The resting supine heart rate in LHT was elevated 82 vs 66 beats/min ($P < 0.0005$) All but 3 patients had resting rates of 75 beats/min or greater those 3 also maintained lower than average rates with both inspiration and expira tion All but 3 controls had resting rates below 75 beats/min those 3 maintained higher than aver age rates with both inspiration and expiration

On statistically contrasting the two groups LHT patients achieved a higher mean rate with inspiration than normals 88 versus 80 beat minute $P < 0.025$ but because they started from a higher baseline their higher absolute rate reflected a very highly significantly lower per centage increase in heart rate than normal 9 versus 22% $P < 0.0005$ The highest percentage increases in both normals and LHT occurred in those individuals with lower than average rest g rates With expiration the LHT group decreased their mean rate only 4% from its resting value whereas normals decreased theirs by 17% a high ly significant contrast $P < 0.0005$ Only two of the LHT group decreased their rate by more than 8% all but three of the normals decreased their rate by more than 8% and all but five by more than any patient

On statistically studying alterations of heart rate within each group separately significant changes are largely limited to the normal con trols They very significantly ($P < 0.001$) increased their heart rate with inspiration from 66 to 80 beats/minute and then decreased it to 54 beats/minute with expiration a significant decrease as compared to their resting rate ($P < 0.0025$) and a very significant decrease com pared to their peak inspiratory heart rate $P < 0.0005$ Patients did not so decrease their rate their change with inspiration was not signif icant $P > 0.05$ and their change with expiration was also not significant when compared to their resting rate and was only barely so ($P < 0.05$) when compared to their peak inspiratory rate

Discussion

This study describes a particular physiologic characteristic of a group of patients with marginal or borderline blood pressure levels associated with unmistakable lability. When compared to normals the lack of heart rate response to a deep breath in LHT was distinctive. While LHT patients at rest started with a more rapid pulse 82 beats/minute vs 66 beats/minute for normals (P < 0.0005) their pulse rate neither increased significantly with inspiration nor decreased with expiration as compared to its resting level P > 0.05 (see Table II). Normal subjects on the other hand very significantly (P < 0.0005) increased their heart rate 22% on inspiration and decreased it 17% on expiration (P < 0.0025) as compared to its resting value. Their rate at peak inspiration only equalled the mean resting rate of LHT patients who maintained a more rapid but unchanging rate throughout inspiration and expiration. Whereas normal subjects demonstrated a rather marked expiratory pause or relative bradycardia of 54 beats/minute or a 17% mean decrease P < 0.0005 patients decreased their rate only 4% to a mean rate of 79 beats/minute an insignificant decrease P > 0.05. These highly significant differences of heart rate responses to a deep breath clearly separate patients with LHT from normal subjects.

While the normal phasic alteration of pulse rate with ventilation is known to lessen with age that was not felt to be an important consideration here because of the seven controls over age 42 five decreased their expiratory pulse rate by 10% or more of the seven patients *less* than age 42 this degree of expiratory slowing was accomplished by only one.

Two particular precautions were observed. By performing the inhalation test a minimum of three times each effort being separated by at least eight to 10 heart beats possible variations ascribable to the slow vasomotor undulations of peripheral arterial pressure of Traube Hering similarly reported in both sleep and wakefulness and extending considerably beyond a single respiratory cycle were minimized.[1] Also the breath test performed in this study was rather rapid and deep but patients carefully refrained from gasping thus avoiding the associated peripheral vascular constrictive spinal reflex known to be unrelated to baroreceptor mechanisms but with decreased handflow often lasting more than a minute and possibly influencing other vasomotor adjustments.[13]

A deficit of heart rate control during a deep breath in patients with LHT has not been previously reported and the associated pathophysiology must remain conjectural until more sophisticated study is applied. Interpretation of these mean group percentage changes must be tempered because the groups started from different resting heart rate baseline values. That this blunted responsiveness is suggestive of physiological uniqueness in LHT however is deduced from the observation that even in the three patients with resting heart rates less than the control average 57 64 and 64 beats/minute each had an expiratory pause of far lesser degree 5 5 and 2% than the control mean decrease of 17%. Additionally the two controls with resting rates greater than the patient average 86 and 91 beats/minute each had expiratory rate decreases 31 and 37% far greater than the patient mean decrease of 4%.

The higher resting pulse rate in LHT reported here has been well documented elsewhere and has been attributed to high indices of sympathetic nervous system activity[7] low indices of parasympathetic cardiac inhibition[9] and a resultant hyperkinetic circulation with enhanced myocardial contractility high cardiac output and peripheral resistances adjusted excessively upward for any given cardiac output. Engrafted upon this abnormal milieu it would appear probably that several described neural and hemodynamic factors attendant upon taking a deep breath working separately or in concert are fundamental in producing the results reported here. Thus such an inspiration promptly increases venous return to the right heart with an increase in right ventricular stroke output of about 25%. As the associated increase in inspiratory capacity of the pulmonary vessels is more than sufficient to absorb the increase in right heart output an increment of blood is effectively withheld from the left ventricle with a resulting slight decrease in its size and of its stroke output by about 7%. This with the associated slight increase in volume capacity of the thoracic aorta in inspiration decreases systolic pressure with deep inspiration about 10% in normal subjects but as much as 30 mm Hg in patients with chronic

obstructive pulmonary disease Heart rate similarly fluctuates with ventilation increasing about 5% with quiet ventilation but to as much as 30% in normal subjects during deep inspiration This has been ascribed to the inspiratory aspiration of blood into the right heart activating the Bainbridge reflex to activation of baroreceptor mechanisms and to some spill over from the respiratory center into the vasomotor center with resultant phasic alteration of sympathetic and vagal efferent traffic to the heart The final degree of heart rate increase and peripheral blood pressure decrease during inspiration and conversely during expiration is the resultant vector of these several factors

Arterial baroreceptor dysfunction has been firmly established in hypertension and is expressed by shifting of response curves to the right with decreased sensitivity and upward resetting While the intensity of the defect correlates with the duration of known hypertensive disease some degree of resetting becomes established very early in hypertension certainly in less than days perhaps even hours and well before light or electron microscopic damage of arterial receptor sites suggesting to some its primacy in hypertension rather than involvement as a secondary phenomenon This early loss of function without discernible structural change coupled with the fact that cardiac vagal efferent traffic ceases about 0 5 seconds *before* commencement of active inspiratory chest motion or phrenic nerve discharge suggests an important role for central factors

In addition to this cessation of cardiac vagal activity inspiration causes an abrupt onset of pre and postganglionic sympathetic discharge activity at all spinal levels including cardiac renal and splanchnic sites Perhaps this additional inspiratory adrenergic contribution was less influential among the LHT group reported here where basal sympathetic tone is already high thereby blunting the otherwise expected increase of heart rate with inspiration as reported here Also to be considered however is the exaggerated degree of adaptive tachyphylaxis acting via a decreased number of active adrenergic receptors reported in the setting of a hyperadrenergic state as well as possible blunting of the aforementioned baroreceptor mechanisms in response to the stimulus of inspiration

Expiration causes an abrupt enhancement of cardiac efferent vagal traffic with only a brief central delay of 50 to 100 msec and a reduction of visceral efferent sympathetic vasomotor activity Thus the expiratory pause in heart rate would appear to be predominantly a parasympathetic cardiac event and in the study reported herein disclosed even greater heart rate abnormalities in LHT than inspiration This lends support to previous evidence of a severe impairment of cardiac parasympathetic inhibition in LHT an impairment similarly noted in sustained essential hypertension and in a variety of non hypertensive organic heart diseases

Medullary and supramedullary influences markedly alter autonomic nervous system control of the heart and under certain experimental circumstances in animals can produce a state of borderline hypertension characterized by marked daytime pressure lability rapid heart rate and circulatory hyperresponsiveness to such non noxious everyday stimuli as moderate noise light and vibration—all rather suggestive of human LHT Whether this abnormal deep breath test reported here in LHT is reflective of such pathogenesis and whether this carries predictive significance concerning subsequent development of sustained hypertension awaits sophisticated study and long term prospective observation

Summary

A group of patients with borderline or labile hypertension were prospectively recruited and asked to take a deep breath while lying supine and being monitored by electrocardiography Their attenuated heart rate responses were sharply abnormal demonstrating an excessively rapid rate throughout but without quickening on inspiration nor slowing with expiration It is suggested that this further demonstrates inadequate autonomic control sympathetic and parasympathetic of the heart in labile hypertension and even at a moment when the patient s blood pressure is normal

The author gratefully acknowledges the statistical assistance of Kathleen Harris (Northwestern University Medical School) and the assistance of Messrs Harvey Denham and Andrew Johnston

REFERENCES

1 Kaplan N Clinical Hypertension 2nd ed Baltimore 1978 The Williams & Wilkins Company

2 Julius S Clinical and physiologic significance of borderline hypertension at youth Pediatr Clin North Am 25 35 1978
3 Pickering G Hi h Blood Pressure 2nd edition New York 1968 Grune & Stratton Inc
4 Hull D H Wolthuis R A Cortese T Longo Jr M S and Triebwasser J H Borderline hypertension versus normotension Differential response to orthostatic stress Am HEART J 94 414 1977
5 Bourne H R Thomson P O and Melmon K L Diagnosis and treatment of beta adrenergic receptor hyperresponsiveness A critical appraisal Arch Intern Med 125 1063 1970
6 Julius S Borderline hypertension An overview Med Clin North Am 61 495 197
7 Weiss Y A Safar M E London G M Simon A C Levenson J A and Milliez P M Repeat hemodynamic determinations in borderline hypertension Am J Med 64 382 1978
8 Frohlich E D and Pfeffer M A Adrenergic mechanisms in human hypertension and in spontaneously hypertensive rats Clin Sci Mol Med 48 225 1975
9 Julius S Pascual A V and London R Role of parasympathetic inhibition in the hyperkinetic type of borderline hypertension Circulation 44 413 19 1
10 Guyton A C Textbook of Medical Physiology 5th edition Philadelphia London Toronto 1976 W B Saunders Company pgs 214 and 272
11 Baust W and Bohnert B The regulation of heart rate during sleep Exp Brain Res. 7 69 1969
12 Lauson H D Bloomfield R A and Courand A The influence of the respiration on the circulation in man with special reference to pressures in the right auricle right ventricle femoral artery and peripheral veins Am J Med 1 315 1946
13 Sharpey Schaefer E P Effect of respiratory acts on the circulation *in* Handbook of Physiology Sect 2 Circulation Vol 3 Washington D C 1965 American Physiological Society
14 Esler M Zweifler A Randall O Julius, S and DeQuattro V Agreement among three different indices of sympathatic nervous system activity in essential hypertension Mayo Clin Proc 52 379 19 7
15 Korner P I Shaw J Uther J B West M J McRitchie R J and Richards J E Autonomic and non autonomic circulatory components in essential hypertension in man Circulation 48 107 19 3
16 Takeshita A Tanaka S Kuroiwa A and Nakamura M Reduced baroreceptor sensitivity in borderline hypertension Circulation 51 38 19 5
1 Mancia G Ludbrook J Ferrari, A Gregorini L and Zanchetti A Baroreceptor reflexes in human hypertension Circ Res 43 1 0 1978
18 Kirchheim H R. Systemic arterial baroreceptor reflexes Physiol Rev 56 100 1976
19 Wallace J M Hemodynamic lesions in hypertension Am J Cardiol 36 670 1975
20 Ito C S and Scher A M Regulation of arterial blood pressure by aortic baroreceptors in the unanesthetized dog Circ Res 42 230 1978
21 Andersen M C Krauhs J M and Brown A M Relationship of aortic wall and baroreceptor properties during development in normotensive and spontaneously hypertensive rats, Circ Res 43 728 1978
22 Sleight P Robinson J L. Brooks D E., and Rees P M Characteristics of single carotid sinus baroreceptor fibers and whole nerve activity in the normotensive and hypertensive dog Circ Res. 41 750 19
23 Katona P G Poitras J W Barnett G O., and Terry B S Cardiac vagal efferent activity and heart period in the carotid sinus reflex Am J Physiol 218 1030 19 0
24 Gootman P M and Cohen M I Efferent splanchnic activity and systemic arterial pressure Am J Physiol 219 897 1970
25 Koizumi K Seller H Kaufman A and Brooks C McC Pattern of sympathetic discharges and their relation to baroreceptor and respiratory activities, Brain Res 27 281 1971
26 Mukherjee C Caron M G and Lefkowitz R J Catecholamine induced subsensitivity of adenylate cyclase associated with loss of beta adrenergic receptor binding sites Proc Natl Acad Sci U.S.A 72 1945 19 5
27 Goldstein R E Beiser G D Stampsfer M and Epstein S E Impairment of autonomically mediated heart rate control in patients with cardiac dysfunction Circ Res 36 571 1975
28 Eckberg D L. Drabinsky M and Braunwald E Defective cardiac parasympathetic control in patients with heart disease N Engl J Med 285 877 1971
29 Conomy J P., Barnes K L., and Ferrario C M The brain and arterial hypertension New direction in an old relationship Neurology 28 1203 19 8
30 Nathan M A and Reiss D J Chronic labile hypertension produced by lesions of the nucleu tractus solitarii in the cat Circ Res 40 72 1977
31 Gebber G L., and Snyder D W Hypothalamic control of baroreceptor reflexes Am J Physiol. 218 124 1970
32 Hallback M and Folkow B Cardiovascular responses to acute mental stress in spontaneously hypertensive rats, Acta Physiol Scand 90 684 19 4

Effect of norepinephrine on coronary hemodynamics in coronary stenotic canine model

Paul Walinsky M D
William Santamore Ph D *
Leslie Wiener M D
Sang Yon Cho M D
Albert N Brest M D
Philadelphia Pa

Although the effect of norepinephrine on coronary hemodynamics has been studied utilizing a variety of experimental models[1] the coronary dynamic effect of norepinephrine in the presence of coronary arterial stenosis has received only limited study Several studies have been directed at this question but have involved the systemic administration of norepinephrine [*] Results thus obtained reflect both direct effects on the heart and the influence of systemic changes induced by norepinephrine In order to evaluate the direct effect of norepinephrine in the presence of coronary artery stenosis we have studied the coronary dynamic effect of intracoronary administration of norepinephrine in the presence of partial coronary artery occlusion We have found a significant decrease in coronary flow after norepinephrine in our canine model of coronary stenosis In order to clarify the mechanism of decreased flow we subsequently studied the coronary response to norepinephrine in the stenotic model with prior alpha and beta receptor blockade These studies suggested an interaction between the peripheral vasculature and the stenotic site and further suggested that the stenosis was not fixed but rather was dynamic In order to clarify the proposed mechanism two further studies were performed—administration of isoproterenol in the canine model and in vitro stimulation of the proposed interaction between stenosis and peripheral vasculature In this paper we report our observations of an adverse effect of β adrenergic stimulation in the model of coronary artery stenosis which may exacerbate myocardial ischemia beyond that induced by an increase in myocardial oxygen demand

From th Department of Med [illegible] Th ma Jeff rso Univers ty Hospital, Ph l d lph

*The study was supported in pa [illegible] In estigato ship to D S ntamore from th A H rt Association
Recei ed for publ c tion Feb 15 l
Accepted f r publ cation M rch 13 l

Reprint requests Dr Paul Walin ky [illegible] J ff rson Uni rsit H sp tal, D ision of Card log 111 S [illegible] Ph l d lphia I 1910

Methods

Animal studies were performed upon 2? mongrel dogs weighing between 29 5 to 34 1 kg All animals were pretreated with morphine 1 mg /kg anesthetized with alpha chloralose 100 mg /kg and were mechanically ventilated Supplemental doses of alpha chloralose were given as needed Arterial blood PO PCO and pH were periodically monitored throughout the experiment using a blood gas analyzer (Instrumentation Laboratory Model 113 Lexington Mass) Respiratory adjustments and/or intravenous infusions of sodium bicarbonate were instituted when necessary to maintain pH between 7 3 and 7 45 PO greater than 60 mm Hg and PCO between 32 and 42 mm Hg The heart was exposed through a left lateral thoracotomy and was suspended in a pericardial cradle A catheter was advanced retrograde from the right femoral artery and positioned in the ascending aorta to

000? 8 03/80/040131 + 07$00 90/0 © 1980 The C V Mosby Co

measure aortic pressure Coronary flow was measured with an electromagnetic flow probe (Biotronex BL610 Silver Springs Md) Depending upon the coronary anatomy the flow probe was placed around the left anterior descending artery or the circumflex artery If the left anterior descending artery was utilized the site of isolation varied from the proximal to the midportion of the artery If the circumflex artery was utilized the site of isolation was proximal to the first major marginal branch

A variable snare type occluder was placed distal to the flow probe The snare consisted of a 1 mm wide band of Teflon passed around the artery through stiff tubing and attached to a machinist s micrometer The snare could be closed by small precise amounts according to a 0 01 mm micrometer scale Distal to the micrometer adjusted snare occluder a 1 0 silk suture was placed around the coronary artery The ends of the suture were inserted through a piece of polyethylene tubing 3 cm in length Zero flow was obtained 2 minutes after each norepinephrine or isoproterenol injection by pulling the ends of the suture while pressing on the polyethylene tubing against the coronary vessel Calibration of the electromagnetic flow probe was performed by timed collections of blood in a graduated cylinder Distal to the occluders a 22 gauge 1 inch angio cath (Deseret Pharmaceutical Co Inc Sandy Utah) was inserted into either a diagonal branch or directly into the circumflex artery This catheter was utilized to monitor distal coronary arterial pressure All norepinephrine or isoproterenol injections were through this cannula

In the region perfused by the instrumented artery a small platinum electrode was inserted into the myocardium to measure an intramyocardial electrogram In three animals wall motion was monitored by a mercury in silicone rubber segmental length gauge Aortic pressure coronary blood flow coronary pressure distal to the snare segmental wall motion and the intramyocardial electrogram were recorded on an Electronics for Medicine physiologic recorder Model DR8

Distal coronary resistance was calculated by dividing mean distal coronary artery pressure by mean coronary blood flow Stenotic resistance was calculated by dividing the mean pressure gradient across the stenosis by mean coronary flow The mean pressure gradient across the stenosis was calculated as mean aortic blood pressure minus mean distal coronary artery pressure Pressure transducers were calibrated by manometer and were determined to be equally sensitive Statistical analysis was performed by comparing the values prior to drug administration to the values obtained following drug infusion by Student s t test [10]

All norepinephrine or isoproterenol injections were through the catheter used to monitor distal coronary arterial pressure Norepinephrine or isoproterenol injections were of 1 μg diluted to 1 ml with physiologic saline administered rapidly and followed by a flush of 0 5 ml physiologic saline This quantity of physiologic saline did not have a measureable effect on coronary pressure or flow All physiologic parameters were recorded continuously for a 10 minute period before and after the injection

In seven dogs the effects of intracoronary injection of norepinephrine were examined before and after partial constriction of the coronary artery Following the injection of norepinephrine in the unstenosed artery 30 minutes were allowed for recovery Subsequently the snare occluder was gradually tightened until mean distal coronary pressure was reduced to approximately 60 mm Hg After a 15 minute period to determine stability at this point norepinephrine was again injected

In seven additional dogs the effects of intracoronary isoproterenol were examined before and after partial coronary artery constriction utilizing the methods outlined above

In four dogs beta blockade was accomplished by administration of propranolol 1 mg /kg intravenously The effects of norepinephrine were examined before and after partial constriction of the coronary artery as outlined above In the remaining four dogs the effects of norepinephrine were studied after alpha blockade with phenoxybenzamine 1 mg /kg intravenously again using the protocol outlined above Beta blockade was verified by the failure of heart rate to change following an intravenous isoproterenol (5 μg) injection at the beginning and end of the experiment Alpha blockade was verified by the decrease in systemic arterial pressure following an intravenous epinephrine (2 5 μg) injection at the beginning and end of each experiment

All injections of norepinephrine were performed after the animal was observed to be stable

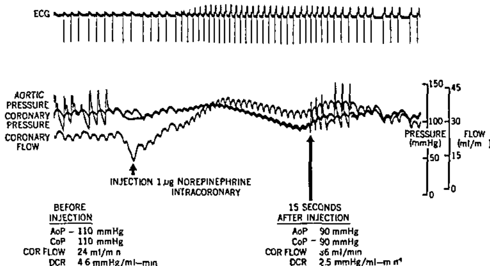


Fig 1A The coronary dynamic response to norepinephrine in the absence of coronary artery stenosis An increase in coronary flow and decrease in distal coronary resistance (*DCR*) are demonstrated at 15 second after injection of norepinephrine

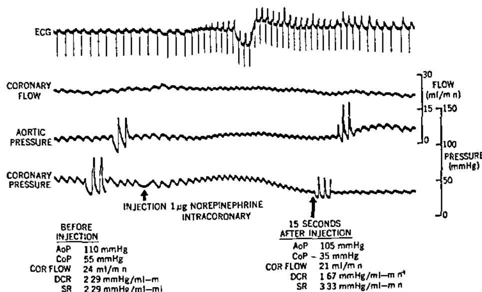


Fig 1B The coronary dynamic response to norepinephrine in the presence of coronary artery stenosis A decrease in coronary flow and distal coronary pressure (*COP*) and increase in stenotic resistance (*SR*) are demonstrated at 15 seconds after injection of norepinephrine

over a 10 minute period Measurement of parameters was made just prior to drug injection and at 7 5 15 30 60 and 120 seconds after each injection

To test if similar changes in stenotic resistance could be induced in vitro a constant flow system was utilized In five dogs the left and right carotid arteries were rapidly removed after killing the animal The arteries were frozen in physiologic saline until they were studied In each study after thawing the artery was attached to the perfusion system and stretched to its original length The artery was kept moist by externally applying physiologic saline A Harvard syringe pump was utilized to maintain a constant flow rate of 22 9 c c per minute The Harvard syringe pump was connected by tubing to the arterial segment (inflow) The other end of the arterial segment (outflow) was connected to tubing to which a rotating three way stopcock was attached The stopcock had a 20 gauge (inner diameter 0 025 inch) cannula on one port and a 16 gauge (inner diameter 0 050 inch) cannula on another port Flow through the stopcock could

Table I Coronary hemodynamic effects of norepinephrine

	Coronary pressure (mm Hg)	*Coronary flow (ml/min)*	*Coronary resistance (mm Hg/ml min)*	*Stenotic resistance (mm Hg/ml min)*
Before occlusion				
Before norepinephrine	113 6 ± 4 4†	31 5 ± 2.5	3 80 ± 0 39	
After norepinephrine				
7 5 seconds	116 9 ± 5 0	35 3 ± 2 1	3 42 ± 0 30	
15 seconds	105 0 ± 4 7	36 4 ± 2 8	3 01 ± 0 27	
30 seconds	113 4 ± 5 0	32 9 ± 2 8	3 67 ± 0 40	
60 seconds	115 3 ± 4 0	30 7 ± 3 6	4 20 ± 0 58	
120 seconds	116 7 ± 3 4	30 3 ± 3 5	4 18 ± 0 54	
After partial occlusion				
Before norepinephrine	58.8 ± 1.3	29 8 ± 3 4	2 19 ± 0 25	2 04 ± 0 26
After norepinephrine				
7 5 seconds	51 0 ± 1.9	24 7 ± 3 3	2 2 ± 0 30	2 86 ± 0 42
15 second	38 8 ± 2 6	22 9 ± 3 6	2 01 ± 0 27	4 25 ± 2 66
30 seconds	37 5 ± 2 7	21 6 ± 3 9	2 13 ± 0 33	4 79 ± 1 16
60 seconds	40 6 ± 3 0	21 0 ± 4 1	2.60 ± 0 54	5 38 ± 1 55
120 seconds	39 7 ± 3 0	23 4 ± 5 2	2 28 ± 0 40	5 12 ± 1 53

Ch nges fr m pre n rep n ph t s gn fi ant t $p < 0\ 05$ by Stud nt t test
All data lues mea ± t d rd rro of m an

then be directed through either a 20 gauge cannula alone (high peripheral resistance) or through both a 20 gauge and 16 gauge cannulae (low peripheral resistance) An isotonic dextran solution (1 7 centipoise) flowing from the syringe pump through the arterial segment would then have either high or low resistance outlets A circumferential snare was placed around the arterial segment Various degrees of stenosis were established with stenotic resistances varying between 1 0 and 6 0 mm Hg/ml min Initial values were recorded during flow through the high resistance outlet Pressures were recorded proximal and distal to the stenosed arterial segment The stopcock position was then changed to allow flow additionally through the 16 gauge cannula needle simulating a low peripheral resistance Proximal and distal pressures were again recorded The stopcock was then closed allowing flow only through the 20 gauge Longdwel needle If the stenotic resistance or pressure gradient across the stenosis did not return to within 5% of the control value the data values were discarded

Results

Fig 1 shows the typical response to norepinephrine Prior to coronary artery constriction (Fig 1A) norepinephrine caused a coronary blood flow increase and a distal coronary resistance decrease After partial coronary artery constriction norepinephrine caused a strikingly different response (Fig 1B) Distal coronary pressure and resistance decreased Although the distal coronary resistance decreased the coronary blood flow decreased This coronary blood flow decrease was associated with a large stenotic resistance increase Table I summarizes the effects of intracoronary norepinephrine (1 μg) in seven experiments Prior to coronary artery constriction norepinephrine caused a slight coronary blood flow increase and distal coronary resistance decrease After partial coronary artery constriction norepinephrine caused a marked decrease in distal coronary pressure and coronary blood flow Distal coronary resistance decreased slightly The coronary blood flow decrease was associated with a large stenotic resistance increase

Table II summarizes the effects of intracoronary norepinephrine in four experiments after beta adrenergic blockade with propranolol Prior to coronary artery constriction norepinephrine caused a significant coronary blood flow decrease and distal coronary resistance increase at 7 5 seconds Beyond that point there were cant changes After partial corr constriction norepinephrine caused a increase in distal coronary pressure coronary resistance at 7 5 second blood flow decreased slightly A

Table II Coronary hemodynamic effects of norepinephrine after beta adrenergic blockade

	Coronary pressure (mm Hg)	Coronary flow (ml/min)	Coronary resistance (mm Hg/ml min)	Stenotic resistance (mm Hg/mL min)
Before occlusion				
Before norepinephrine	113.8 ± 3 2†	30 0 ± 0 7	3 83 ± 0 11	
After norepinephrine				
7.5 seconds	115 5 ± 3 6	22 0 ± 2 6	5 69 ± 0 81	
15 seconds	118 8 ± 2 7	33 2 ± 2.2	3 64 ± 0.30	
30 seconds	116 2 ± 3 2	29 6 ± 1.5	4 00 ± 0.20	
60 seconds	117.5 ± 4 1	28 1 ± 1.3	4 21 ± 0 12	
120 seconds	117.5 ± 4 1	29 0 ± 0.9	4 07 ± 0 09	
After partial occlusion				
Before norepinephrine	61 8 ± 1 0	25 4 ± 0.9	2 45 ± 0 10	1.99 ± 0 [illegible]
After norepinephrine				
7.5 seconds	88 8 ± 4.5	20.5 ± 2.5	4 16 ± 0 72	0 88 ± 0.37
15 seconds	59 2 ± 4 1	23.8 ± 1.3	2 53 ± 0.21	1.88 ± 0 4
30 seconds	60 0 ± 5.9	25 5 ± 1 2	2 40 ± 0.27	2.04 ± 0 49
60 seconds	65 0 ± 2 5	25 4 ± 1 4	2 61 ± 0 21	1.90 ± 0 34
120 seconds	63 8 ± 4.8	25 4 ± 0 9	2.50 ± 0 09	2.0 ± 0.35

Changes from pre-norepinephrine value significant at $p < 0.05$ by Student's t test
†All results are expressed as mean ± SEM

Table III Coronary hemodynamic effects of norepinephrine after alpha adrenergic blockade

	Coronary pressure (mm Hg)	Coronary flow (ml/min)	Coronary resistance (mm Hg/ml min)	Stenotic resistance (mm Hg/mL min)
Before occlusion				
Before norepinephrine	107.5 ± 3 8†	42 7 ± 6 8	2 77 ± 0 48	
After norepinephrine				
7 5 seconds	100 0 ± 6 3	64 2 ± 12 3	1 77 ± 0 28	
15 seconds	99.5 ± 1.8	63 8 ± 9 1	1 65 ± 0 18	
30 seconds	113 0 ± 5 2	54 6 ± 7 6	2 20 ± 0 26	
60 seconds	107.5 ± 6.5	47 1 ± 9 6	2 61 ± 0 49	
120 seconds	108 8 ± 6 2	50 4 ± 8.8	2 38 ± 0.38	
After partial occlusion				
Before norepinephrine	55 0 ± 2.5	30 2 ± 1.9	1.86 ± 0 15	1.50 ± 0 19
After norepinephrine				
7.5 seconds	51.8 ± 1 7	30 0 ± 2.9	1 75 ± 0 12	1.81 ± 0 19
15 seconds	44 2 ± 2 9	26 0 ± 1 5	1 70 ± 0 06	2.25 ± 0 61
30 second	39 5 ± 4 7	25 4 ± 2.2	1.53 ± 0 05	2 67 ± 0 81
60 seconds	39 2 ± 5 8	26 2 ± 0.5	1 61 ± 0 12	2.34 ± 0.59
120 seconds	42 5 ± 5 2	25.2 ± 1.8	1 72 ± 0 06	2.31 ± 0 67

Changes from pre norepinephrine al gn f n t $p < 0.05$ by Stud nt t test
†All results are expressed as m an SEM

decrease in stenotic resistance was encountered at the same time period Thus beta adrenergic blockade by propranolol prevented the distal coronary pressure decrease and stenotic resistance increase that had occurred after norepinephrine

Table III summarizes the effects of intracoronary norepinephrine in four experiments after alpha adrenergic blockade with phenoxybenzamine Prior to coronary artery constriction, norepinephrine caused a large coronary blood flow increase and distal coronary res[illegible]

Table IV Coronary hemodynamic effects of isoproterenol

	Coronary pressure (mm Hg)	*Coronary flow (ml/min)*	*Coronary resistance (mm Hg/ml min)*	*Stenotic resistance (mm Hg/ml min)*
Before occlusion				
Before norepinephrine	1?3 6 ± 1 4	30 6 ± 1 0	4 2? ± 0 14	
After norepinephrine				
7 5 seconds	121 6 ± 1 4	10?3 ± 3 ?	1 31 ± 0 0	
15 seconds	11?0 ± 2 1	100 5 ± ? ?	1 15 ± 0 04	
30 seconds	109 3 ± ? 5	60 3 ± ? 9	1 9? ± 0 0?	
60 seconds	119 6 ± 1 6	39 9 ± 1 7	3 ?4 ± 0 1?	
1?0 seconds	1??9 ± 1 4	33 4 ± 1 1	3 89 ± 0 14	
After partial occlusion				
Before norepinephrine	63 6 ± 1 2	20 8 ± 0 4	3 0? ± 0 04	3.01 ± 0 29
After norepinephrine				
5 seconds	46 1 ± 2 3	19 0 ± 0 9	2 5? ± 0 11	5 11 ± 0 94
15 seconds	38 9 ± 1 4	16 8 ± 0 9	2 60 ± 0 13	6 26 ± 1 54
30 seconds	3?6 ± 1 9	14 7 ± 1 0	? 58 ± 0 13	6 89 ± 1 33
60 seconds	3?4 ± 2 3	1? ? ± 1 0	?91 ± 0 15	?81 ± 1 33
1?0 seconds	39 0 ± ?1	13 ± 1 0	3 2? ± 0 ?0	8 92 ± 2 46

p ≤ 0 0 chang f om p e injecti n alue Student t test
†All data alue mean ± tandard err r of m an

Table V Effects of peripheral resistance changes on stenotic resistance in an in vitro constant flow stenosed carotid artery preparation

Peripheral resistance (mm Hg ml min)	*Pr ximal pres ure (mm Hg)*	*Distal pressure (mm Hg)*	*Stenotic resistance (mm Hg/ml min)*
5 19 ± 0 0?†	15? ± 4	118 8 ± 1 4	1 60 ± 0 10
0 0 ± 0 0?	164 4 ± 18 5	16 1 ± 0 4	6 47 ± 0 82

p 0 01 a mpa ed t cont l by Student s t te t
†All d ta alues m an ± stand d rror of m an

decrease After partial coronary artery constriction norepinephrine caused a large distal coronary pressure decrease and a slight decrease in the distal coronary resistance Although the distal coronary resistance decreased the coronary blood flow decreased This coronary blood flow decrease was significantly ($p < 0\ 05$) different from the response to norepinephrine in the animals without stenosis and was associated with the stenotic resistance increase Thus alpha adrenergic blockade by phenoxybenzamine did not prevent the distal coronary pressure decrease and stenotic resistance increase that occurred after norepinephrine

Mean aortic pressure and heart rate did not change significantly following norepinephrine in any of the above groups

Table IV summarizes the effects of intracoronary isoproterenol in seven experiments and represents further evidence for a beta receptor mediated response as the mechanism for the changes seen following norepinephrine Prior to coronary artery constriction isoproterenol caused a large coronary blood flow increase and a coronary resistance decrease After partial coronary artery constriction isoproterenol caused a large distal coronary pressure decrease and a slight distal coronary resistance decrease Although the distal coronary resistance decreased the coronary blood flow decreased This coronary blood flow decrease was significantly ($p < 0\ 05$) different from the normal response to isoproterenol and was associated with a large stenotic resistance increase In this group mean aortic

pressure was unchanged but heart rate increased significantly following isoproterenol

Table V suggests that the stenotic resistance changes are related to alteration of peripheral coronary resistance and intraluminal changes in pressure Table V summarizes the results of the in vitro constant flow experiments and is based upon 51 observations in seven arteries Lowering the peripheral resistance in a constant flow system caused an obvious reduction in the distal pressure Reducing the distal pressure always caused stenotic resistance to increase This *stenotic resistance increase caused the proximal* pressure to increase, although the peripheral resistance had been greatly reduced Further these stenotic resistance changes were bidirectional lowering the distal pressure increased the stenotic resistance while increasing the distal pressure decreased the stenotic resistance

Discussion

The effect of norepinephrine administered into the unobstructed coronary artery reflects both alpha and beta adrenergic receptor responses [11] The net effect in our study was a slight transient decrease in coronary vascular resistance followed by a minimal increase in resistance at one to two minutes following injection These findings are similar to those reported by others and are presented primarily for the purpose of comparing the coronary vascular response to norepinephrine before and after partial coronary artery constriction In the setting of severe partial coronary artery constriction dramatic differences in response were noted Thus following intracoronary administration of norepinephrine a decrease in coronary blood flow and distal coronary pressure with an increase in stenotic resistance were documented This response was not seen following pretreatment with propranolol suggesting beta receptor stimulation as the mediator of this response Alpha adrenergic blockade with phenoxybenzamine did not alter this response Further beta adrenergic stimulation with isoproterenol caused a similar decrease in coronary blood flow and distal coronary pressure and an increase in stenotic resistance

Several potential mechanisms for the observed stenotic resistance increase after norepinephrine were not substantiated by our findings We initially considered the possibility of an alpha adrenergic induced vasoconstriction at th the snare However in animals pretreat propranolol the alpha adrenergic respo manifested as an increase in coronary r decrease in coronary flow and decrease ir ic resistance (Table II) These changes group were only transient with a pea noted at 7 5 seconds and with subseque return to control values Thus there increased stenotic resistance in this g animals Furthermore the phenoxybe pretreated animals had a response simila *of the animals without adrenergic b* Alpha adrenergic stimulation is thus unl the mechanism of the coronary flow decr stenotic resistance increase

An increase in turbulence consequent epinephrine was also considered After nephrine and isoproterenol coronary bl decreased while stenotic resistance incre the presence of decreased flow it is thus that an increase in turbulence is the cause for the observed stenotic re changes [11]

A decrease in systemic pressure in the p of a critical stenosis could also result in a c flow and distal pressure However such ch systemic pressure was not demonstrated a change in collateral supply to the dista the stenosed artery might also be consid mediate the observed changes Howev potential changes in *collateral blood* would occur in the distal coronary vasc *and therefore could not account for the o* changes in stenotic resistance and decr antegrade coronary flow

It is of note that the stenotic resistance c were also observed in an in vitro carotid preparation This finding is in suppor primary role for the alteration in distal p as a primary cause for the stenotic res changes Although the flow rate was consta stenotic resistance changes were bidirec Lowering the distal pressure and res increased the stenotic resistance *while inc* the distal pressure and resistance decrea stenotic resistance (Table V) This suggests that the stenosis was not fixed but was subject to dynamic alteration rel hydraulic phenomena It also suggests th unlikely that phenomena such as platelet

gation alteration of collateral flow and alteration in flow turbulence were the primary cause for the observed changes in stenotic resistance

We postulate that the initiating event following norepinephrine administration is a beta, and/or beta adrenergic mediated decrease in arteriolar tone leading to an alteration of geometry at the stenotic site Because of proximal high grade narrowing of the coronary artery flow cannot increase pari passu A coronary pressure decrease thus results The norepinephrine induced decrease in distal coronary pressure will result in a decrease in pressure by the stenosis according to Bernoulli s equation This decrease in intraluminal pressure may then lead to a decrease in the effective stenotic area [1] In the presence of an underlying high grade stenosis a minimal decrease in radius will be sufficient to significantly increase stenotic resistance The concept of a passive change in stenotic resistance has been previously described by Schwartz and co workers In addition Logan has demonstrated in in vitro perfused human arteries that vessels with eccentric lesions demonstrate a variable resistance to flow Resistance to flow was inversely related to the perfusion pressure the lower the perfusion pressure the higher the resistance

We have previously demonstrated in the model of coronary stenosis that another stimulus of distal coronary vasodilation transient occlusion of the vessel resulted in a decrease in coronary flow and an increase in stenotic resistance In vitro studies with two types of tubing revealed that these changes were seen with relatively flexible but not with relatively rigid tubing These findings suggested that with some mobility of a portion of a tight stenosis the stenosis demonstrated dynamic rather than fixed hydraulic consequences

We are unable to further confirm the mechanisms we have suggested since the changes in radius which may occur at the stenotic site are beyond the resolution of our current angiographic techniques Nonetheless although we cannot conclusively confirm the mechanisms we have suggested the observation of a coronary flow and pressure decrease and a stenotic resistance increase following norepinephrine demonstrates an adverse effect of beta adrenergic stimulation which may further exacerbate ischemia beyond that induced by an increase in myocardial contractility and an increase in myocardial oxygen demand Prevention of this phenomenon by propranolol is of interest in assessing the mechanism of its development Furthermore it also suggests that in the presence of coronary stenosis propranolol may decrease myocardial ischemia by maintaining coronary flow and pressure in addition to its well recognized mode of action of decreasing myocardial oxygen demand

In conclusion we have documented the response of the coronary vasculature to norepinephrine in the presence of a critical coronary arterial narrowing The response to such intervention mediated by beta adrenergic stimulation results in a significant decrease in coronary flow An increased resistance at the stenotic site is suggested as the likely mechanism This phenomenon may be of importance in the pathophysiology of coronary artery disease

Summary

The effect of intracoronary injection of 1 μ norepinephrine was assessed in 14 open chest dogs anesthetized with alpha chloralose Studies were performed before and after partial coronary artery constriction by a circumferential snare Aortic pressure coronary pressure distal to the stenosis and coronary flow were monitored before and after injection of norepinephrine Calculated values were stenotic resistance and distal coronary resistance Before coronary constriction norepinephrine resulted in an early minimal increase in coronary flow and decrease in distal coronary resistance with prompt return to control values In contrast with high grade coronary constriction at 15 seconds after norepinephrine coronary flow decreased (29 8 ± 3 4 to 22 9 ± 3 6 ml /minute) ($p < 0\ 05$) coronary pressure decreased (58 8 ± 1 3 to 28 8 ± 2 6 mm Hg) ($p < 0\ 05$) and stenotic resistance increased (2 04 ± 0 26 to 4 25 ± 2 66 mm Hg/ml min) ($p < 0\ 05$) without change in heart rate or aortic pressure These changes persisted over a two minute period of observation following norepinephrine In the stenotic model the decrease in coronary pressure and coronary flow and increase in stenotic resistance were blocked by pretreatment with propranolol but not by phenoxybenzamine Administration of isoproterenol resulted in changes similar to those induced by norepinephrine in the stenotic model Simulation of

alteration of peripheral resistance in an in vitro model demonstrated that with a high initial stenotic resistance a decrease in peripheral resistance resulted in an increase in stenotic resistance We conclude that the decrease in coronary pressure following norepinephrine was mediated by beta, or beta adrenergic stimulation We further postulate that the decreased coronary flow and increased stenotic resistance were caused by a passive decrease in radius at the stenotic site

The authors gratefully acknowledge the technical assistance of Mr Stephen Jones and Mr Dominic Dragotta and the assistance of Ms. Marlene Silvagni in preparation of the manuscript

REFERENCES

1. Pose G Adrenergic responses of the coronary vessel Circ. Res. 39 461 1976.
2. Berne R. M Effect of epinephrine and norepinephrine on coronary circulation Circ Res. 6 644 1958
3. Hardin, R A., Scott J B and Haddy F J Effect of epinephrine and norepinephrine on coronary vascular resistance in dogs Am J Physiol. 201 276 1961
4. Parratt J R Blockade of sympathetic β receptors in the myocardial circulation, Br J Pharmacol. 24 601 1965
5. Malindzak, G S Van Dyke A H., Green H D and Meredith, I H Alpha and beta adrenergic receptors in the coronary vascular bed Arch Intern Pharmacodyn Ther 197 112, 1972
6. Denison A. B., Bandhanabaedya S and Green H D Adrenergic drugs and blockade on arterioles and myocardial contraction Circ Res 4 653, 1956
7. Vatner S F McRitchie R J., Maroko P R., Patrick T A. and Braunwald E Effects of cathecholamines, exercise and nitroglycerin on the normal and ischemic myocardium in conscious dogs J Clin Invest 54 563, 1974
8. Mueller H., Ayres, S M Gregory J J Giannelli, and Grace W J Hemodynamics coronary blood and myocardial metabolism in coronary shock Re to l norepinephrine and isoproterenol J Clin. I 49 1885 1970
9. Gould K L Lipscomb K., and Calvert C Comp tory changes of the distal coronary vascular bed d progressive coronary constriction Circulation 51 1975
10. Guilford J P Fundamental Statistics in Psych and Education New York 1965 McGraw Hill Company Inc pp 255-256 and 181 18
11. Mark A L., Abboud F M Schmid P G He D D and Mayer H E Differences in direct effe adrenergic stimuli on coronary cutaneous and mu vessels, J Clin. Invest 51 279 1972
12. Gaal P D., Kattus, A.A Kolin A. and Ross, G E of adrenaline and noradrenaline of coronary bloo before and after beta adrenergic blockade Br J macol 26 713 1966
13. Young D F., Cholvin N R Kirkeeide R. L., and A. C Hemodynamics of arterial stenoses at el flow rates Circ Res 41(1) 99 1977
14. Milnor W R Principles of hemodynamics, in M Physiology Mountcastle V B editor S Louis, The C V Mosby Company pp 914 979
15. Patel, D J and Janicki, J S Static elastic proper the left coronary circumflex artery and the co carotid artery in dogs, Circ Res. 27(?) 149 19?0
16. Mates R E., Gupta R L Bell A C., and Klocke Fluid dynamics of coronary artery stenosis, Cir 42 152, 1978
17. Schwartz J S., Carlyle P F., and Cohn J N I coronary pressure as a determinant of resistance s stenotic coronary arteries, (Abstr) Am J Ca 39 328 1977
18. Logan S E On the fluid mechanics of human cor artery stenosis IEEE Trans Biomed Eng 2 1975
19. Walinsky P., Santamore W P Wiener L., and A. N Dynamic changes in the hemodynamic sever coronary artery stenosis in a canine model Cardio Res. 13 113 1979

Superior vena cava syndrome Case report

A complication of permanent transvenous endocardial cardiac pacing requiring surgical correction

G G Youngson
F N McKenzie
P M Nichol
London Ontario Canada

Thromboembolism of the great veins is an unusual but well documented complication of transvenous endocardial pacing The condition may present as superior vena cava syndrome and such cases have previously responded to conservative management However because of concern about the nature of the lesion and the progression of symptoms in this case surgical intervention was chosen

Case report

A 75-year old woman had a transvenous endocardial pacemaker inserted in 1973 on account of Stokes Adams attacks In November 1977 she developed painless swelling of her face and upper limbs which increased over the ensuing months When she presented in March 1978 her facial and limb swelling were considerable (Fig 1) Cyanosis of her thorax arms and head in association with hoarseness and altered mentation had also appeared in the weeks prior to admission

Examination revealed the mucous membranes of her face to be suffused and macroglossia to be present Telangiectasia was present in the skin over the upper trunk Her neck veins were grossly distended as were the veins in the arms and chest wall Fundoscopy likewise showed venous distension Physical examination was otherwise unremarkable apart from the presence of a short ejection systolic murmur in the aortic area

Laboratory investigations demonstrated normal blood count and biochemistry the electrocardiogram showed incomplete right bundle branch block and satisfactory demand mode of pacemaker function Chest x ray showed slight widening of the upper mediastinum but tomography and gallium scan failed to demonstrate any specific mediastinal lesion Under fluoroscopy however the pacemaker lead did not exhibit the usual sling like action at the superior cavo-atrial junction and appeared to be fixed at this point Superior and inferior vena caval catheterisation demonstrated a shelf like obstruction of the superior vena cava at its junction with the right atrium (Figs 2*a* and 2*b*) A pressure



Fig 1 Preoperative photograph demonstrates marked facial edema Note imprint from spectacle frame

From University Hospital St Joseph's Hospital, and the University of Western Ontario London Ontario Canada

Received for publication Nov 1978

Accepted for publication Dec 15 1978

Reprint requests Dr G G Youngson University Hospital Dept of Cardiovascular and Thoracic Surgery 339 Windermere Rd London Ontario N6G K3, Canada

0002-8703/80/040503 + 03$00 30/0 © 1980 The C V Mosby Co




Fig 2 A and B PA and lateral superior vena cavogram demonstrating stenosis at superior cavo atri junction

gradient of 26 mm Hg was measured between the superior vena cava and right atrium

In view of her age transvenous dilatation of the obstructing lesion was attempted in the first instance However although a balloon catheter could be placed with difficulty within the obstructing segment the obstruction itself was too rigid to allow dilatation by balloon inflation Since she was becoming increasingly symptomatic with facial edema and because of concern about possible cerebral thrombosis surgery was recommended

At operation the heart was exposed through a median sternotomy incision The superior vena cava appeared and felt normal apart from venous hypertension an obvious tumor mass however [illegible] uld be palpated in the upper third of the atrium The patient wa [illegible] nne ted to cardiopulmonary bypass by cannulati [illegible] superior and inferior venae cavae and ascending aorta [illegible] pening the right atrium the lumen between the right atriu [illegible] superior vena cava was seen to be obliterated by a fi [illegible] th thr ugh which passed the endocardial pacem [illegible] An in ision was made through the tumor down [illegible] nd a portion of the tumor like mass was excise [illegible] xamination of the lesion showed myocardial hy [illegible] fibrous tissue and a surface layer of fibrin [illegible] evidence of malignancy

To ensure an adequate lum [illegible] pen av atrial junction pericardium was plac [illegible] h graft onto the lateral atrial wall Pressures w [illegible] ther side f the site of the lesion at the en [illegible] lure and n

gradient could be detected The transvenous lead w[illegible] and was replaced with an epicardial lead

The patient made an uneventful recovery from [illegible] and was discharged home two weeks later relieved symptoms She remains well (follow up 6 months)

Comment

The more common complications of pe[illegible] transvenous endocardial pacing include [illegible] generator pocket infection lead dislo[illegible] cardiac perforation, and lead fracture [illegible] thromboembolism related to the lead occ[illegible] ly but four cases have previously been [illegible] where the venous thrombosis manife[illegible] superior vena cava syndrome All the[illegible] resolved with anticoagulant therapy alth[illegible] one instance streptokinase was used [illegible] long term anticoagulation

The use of anticoagulant or thromboly[illegible] apy would not have effected a cure in our [illegible] since the bulk of the obstructing lesion co[illegible] fibrous tissue This was considered to repr[illegible] unusual tissue response of the endocar[illegible] chronic irritation by the transvenous pac[illegible] lead and with removal of the irritant



Fig 3 Histology of resected specimen demonstrating myocardium with adjacent fibrotic tissue and surface fibrin deposition

was effected with little chance of recurrence

We believe this to be the first report of a fibrotic endocardial lesion associated with an endocardial pacemaker lead manifesting as superior vena cava syndrome

Summary

Superior vena cava syndrome developed in a patient in whom an endocardial transvenous pacemaker had been inserted five years previously Venography demonstrated an obstructing lesion at the junction of the superior vena cava and right atrium Balloon catheter dilatation failed to afford any relief from her progressive symptoms Exploration of the area revealed a benign fibrotic lesion encircling the pacemaker lead within the right atrium Excision of the lesion removal of the lead and patching the right atrium with pericardium resulted in rapid cure

REFERENCES

1 Wertheimer M., Hughes R., and Hilman Castle C Superior vena cava syndrome Complication of permanent transvenous endocardial pacing JAMA 224 1172 1973

2 Williams D R., and Demos, N J Thrombosis of superior vena cava caused by pacemaker wire and managed with streptokinase J Thorac Cardiovasc Surg 68 134 1974

3 Chamaro H, Rao G and Wholey M H Superior vena cava syndrome a complication of transvenous pacemaker implantation Radiology 126 377 1978

Multiple coronary thromboses in previously normal coronary arteries a rare cause of acute myocardial infarction

Edward H Schuster M D
Stephen C Achuff M D
William R Bell M D
Bernadine H Bulkley, M D
Baltimore Md

Most acute myocardial infarcts are associated with atherosclerotic narrowing of the coronary arteries although occasional and relatively infrequent instances of infarction with normal coronary arteries have been described [1] Acute coronary occlusions are most often caused by thrombosis overlying an eroded atherosclerotic plaque but thromboemboli may be a source of acute occlusion of an otherwise normal coronary tree Described here is an unusual patient with previously normal coronary arteries who developed acute thrombosis of the proximal right and left anterior descending coronary arteries which led to a fatal myocardial infarction The role of heparin in the pathogenesis of the coronary thrombi in this particular patient is suggested

Case report

A 44 year old woman with a history of cigarette smoking and mild hypertension was admitted to the hospital for evaluation of vertigo and dysarthria She had been well until one month previously when she developed daily frontal and occipital headaches which occurred upon awakening The headaches would resolve as the day progressed and were unassociated with any visual or neurologic symptoms Sh[e] before admission she felt the room spinning from right to noted visual blurring and a three minute period of sl[urred] speech Her family history was positive for diabetes m[ellitus] hypertension and myocardial infarction She was on [no] medications

Physical examination on admission revealed a tempera[ture] of 99 2 F a pulse of 76 which was regular and a b[lood] pressure of 124/80 Cardiovascular examination was n[ormal] without murmurs rubs or gallops Neurologic examina[tion] was normal except for horizontal nystagmus and mild [left] sided facial weakness Laboratory values on admis[sion] included a normal complete blood count with a platelet co[unt] of 243 000 Chemistries were normal except for a se[rum] cholesterol of 279 The chest radiograph and electrocar[dio]gram were normal. A lupus erythematosus cell preparat[ion] and rheumatoid factor were negative

Hospital course Shortly after admission a lumbar pu[nc]ture and CAT scan (computerized axial tomography of [the] brain) were normal Carotid arteriography showed a stenosis of the left internal carotid artery 2 cm above [the] bifurcation but due to a radiographic contrast reaction [the] right system was not studied With a diagnosis of tra[nsient] ischemic attacks intravenous heparin was instituted and [within] 36 hours there was complete resolution of her [neurologic] symptoms On the tenth hospital day her platelet count [was] 43 000 and heparin was discontinued Within a matter of ho[urs] she developed crushing retrosternal and back pain T[he] electrocardiogram showed changes of an acute inferior m[yo]cardial infarction The patient was transferred to the c[oronary] care unit A repeat platelet count was 1 000 but par[tial] thromboplastin and prothrombin times were not obta[ined] Over the next 24 hours she became hypotensive anuric [and] developed electrocardiographic changes of anterior myoc[ar]dial infarction The patient developed refractory ventricu[lar] fibrillation and died 24 hours after her first episode of ch[est] pain

Autopsy findings At autopsy her heart weighed 3?0 gra[ms] An acute myocardial infarct was present in the an[terior] posterior walls of the left ventricle extending into the sep[tum]

From the Cardiovascular Division of the Department of Medicine and Department of Pathology The Johns Hopkins Medical Institutions Baltimore Md

Supported by Grants P50 HL 1 6 0 and HL 01601 with the National Institutes of Health Public Health Service Department of Health Education and Welfare and the ... Laboratory for Myocardial Research

Received for publication Nov 19 8

Accepted for publication Jan 15 19 9

Reprint requests Bernadine H Bulkley M D Cardiovascular Division The Johns Hopkins Hospital Baltimore Md

0002-8703/80/040506 + 04$00 40/0 © 1980 The C V Mosby Co

and involving a substantial amount of the right ventricle Postmortem coronary arteriography demonstrated occlusion of the left anterior descending coronary artery and the right coronary artery (Fig 1) and fresh thrombus was present in both vessels at the sites of occlusion Histologic examination of the thrombus showed evidence of organization compatible with 12 to 24 hours (Fig 2) There was no arteritis or congenital abnormality of the coronary tree The remainder of the coronary arteries were widely patent without evidence of significant atherosclerosis Examination of the brain showed no hemorrhages infarcts or vascular abnormalities In situ examination of the carotid arteries revealed 50% stenosis of both right and left internal carotid arteries The remainder of the autopsy was unremarkable without evidence of systemic vasculitis or thrombotic lesions elsewhere either in the systemic arteries or in the pulmonary vessels

Discussion

This relatively young woman died of a massive myocardial infarction that involved well over half of her left ventricle and a significant portion of the right ventricle The infarcts occurred in a heart with previously normal coronary arteries in which sudden and apparently simultaneous occlusions of both right and left coronary arteries occurred Her rapidly progressive downhill course with cardiogenic shock and heart block was compatible with the extensive myocardial injury The most peculiar feature of her coronary lesions however was that they were due to thrombotic occlusions of the proximal vessels unassociated with underlying atherosclerosis intimal plaque rupture or other arterial lesions such as vasculitis which might account for the thrombosis

The cause of acute thrombosis in this patient is not entirely clear The most common cause of a thrombotic occlusion of a previously normal coronary artery is embolization Almost always however a source of the embolus can be identified whereas in this patient there was no evidence of thrombotic material on the heart valves or mural endocardium Her coronary lesions were also unusual for embolic phenomena in that both were proximal in location Coronary emboli in three quarters of instances lodge distally in the previously normal coronary vessel and cause generally small although transmural infarcts The massive and fatal myocardial injury in this woman was due to the proximal location of both coronary occlusions leading to loss of most of her left ventricle Also unusual for embolization is the simultaneous involvement of two main coronary vessels Without atherosclerosis intimal injury vasculitis or a source of embolization one must consider that in situ thrombosis of



Fig 1 Postmortem angiogram showing occlusive lesions in left anterior descending (*LAD*) and right coronary arteries (*RC*) By the time of death thrombi in both vessels had retracted restoring flow to the distal vessels The coronary vessels are otherwise widely patent and free of disease

her coronary arteries may be related to the heparin therapy

Coronary artery spasm is a known etiology of myocardial infarction in patients with normal coronary arteries There is at least one documented case in which at autopsy a fresh thrombus was found at the site of angiographically proven spasm and it was suggested that blood stagnation may have resulted in platelet aggregation release of thromboxane A and thrombus deposition at the site of spasm There are however several points which make spasm an unlikely precipitating cause of our patient s multiple thrombi All of the patients with a vasospastic explanation for myocardial infarction had multiple attacks of angina before the infarction whereas our patient had no history of chest pain Of over 200 patients reported with angiographically documented spasm only one[11] had evidence of spasm involving two major coronary arteries Also if spasm leads to coronary thrombosis via the release of thromboxane A from platelets one might question whether this hypothesis is valid

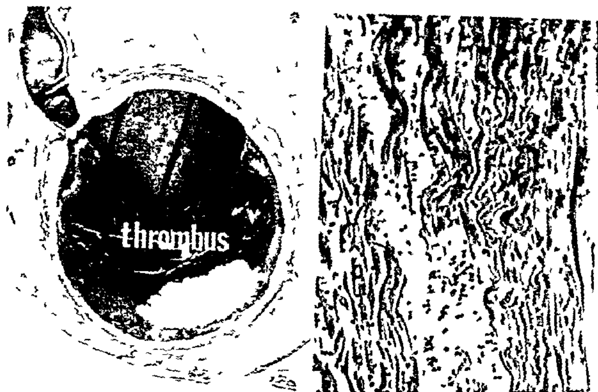


Fig 2 *Shown on the left* is a transverse histologic section from the left coronary artery showing the thrombus within the lumen. The thrombus has partially retracted and angiographic injection mass is seen above it. The coronary vessel is free of atherosclerosis. *Shown on the right* is a section of infarcted left ventricular myocardium in the distribution of the occluded vessel. The thin wavy fiber change and polymorphonuclear infiltrate are compatible with an infarct of 24 hours of age (Hematoxylin and eosin original magnifications—left ×48, right ×175)

a patient with thrombocytopenia Thus although we cannot exclude a vasospastic myocardial infarction in our patient we believe this is unlikely

There is a precedent for thromboembolic phenomena occurring on heparin therapy In 1958 Weismann and Tabin reported 10 cases of peripheral vascular emboli in heparinized patients over a three year span These patients received heparin 150 to 500 mg per day intramuscularly and at autopsy there was no evidence of a cardiac source for the emboli. Roberts and colleagues in 1964 studied 11 cases of surgically proved peripheral emboli in patients on heparin for at least ten days Barker studied 110 cases of arterial embolism and suggested that 12% were induced by heparin therapy Rhodes reported two patients similar to ours who developed myocardial infarction associated with heparin administration Both patients were receiving heparin for thrombophlebitis and had no prior history of cardiac disease On day eight and day ten of heparin therapy respectively these patients had clinical and electrocardiographic changes consistent with myocardial infarction and survived It was postulated that increased platelet aggregation and adhesiveness were the cause of the myocardial infarctions Thus, of the multiple reports of heparin associated vascular thromboemboli we have identified only two patients who have been reported to develop acute myocardial infarction while on heparin for noncardiac reasons Both infarctions occurred after eight days of therapy and were seen in patients who were thrombocytopenic In these latter two patients however angiographic or morphologic confirmation of the coronary lesions was not obtained and whether acute thrombosis within the coronary tree occurred is not known.

These three patients with myocardial infarction in the setting of thrombocytopenia and heparin therapy at least raise the suspicion that the two together or alone related to the infarct. If one considers how vascular thrombosis may occur on heparin therapy it is always possible that inadequate anticoagulation was achieved especially in between doses Another possibility may be related to the thrombocytopenia

disseminated intravascular coagulation that may develop on heparin therapy Bell and coworkers have identified a phenomenon of diffuse intravascular coagulation and thrombocytopenia found in patients on heparin This tends to occur between day 2 and 10 of heparin therapy and takes 3 to 5 days to resolve after heparin is discontinued Although this reaction to heparin has been associated with hemorrhagic problems no documented thrombosis or embolization have occurred If this indeed represents a diffuse intravascular coagulation type of state it would not be surprising to identify thrombotic events in these patients In an autopsy study of diffuse intravascular coagulation from other causes Sugiura and associates found a 20% incidence of coronary thrombosis and a 16% incidence of myocardial infarction It may well be possible therefore that the acute myocardial infarction and acute coronary thrombosis in previously normal coronary arteries that occurred in our patient in association with heparin treatment were a manifestation of coagulopathy That her chest pain occurred within hours of stopping heparin might also suggest a rebound phenomenon from the effects of anticoagulant There is little evidence however that a rebound hypercoagulable state can develop as a consequence of anticoagulant withdrawal Whatever the mechanism one cannot ignore the association of heparin thrombocytopenia with her unusual thrombotic event

More importantly this case does show that the coronary arteries may be a site for acute thrombosis without underlying atherosclerosis arteritis or other vascular pathology Such a case at least raises the possibility that coagulation abnormalities may be responsible for some forms of acute myocardial infarction and that infarcts can occur albeit rarely in patients with previously normal coronary arteries

Summary

This report describes an unusual form of myocardial infarction in a 44 year old woman who was found to have two proximal coronary artery thrombi with otherwise normal coronary arteries. An interesting feature of her history was that the coronary events occurred in association with thrombocytopenia and heparin treatment Two other clinical reports of patients who developed thrombocytopenia and myocardial infarction while receiving heparin have been identified and the possibility that these thrombi were secondary to a coagulation abnormality associated with heparin is considered

REFERENCES

1 Kahn A H and Haywood L J Myocardial infarction in nine patients with radiologically patent coronary arteries N Engl J Med 291 477 1974
2 Prizel K R Hutchins G M, and Bulkley B H Coronary artery embolism and myocardial infarction A clinicopathologic study of 55 patients Ann Intern Med 88 155 19 8
3. Chalmers, T., Matta R Smith M and Kunzler A Evidence favoring the use of anticoagulants in the hospital phase of acute myocardial infarction N Engl J Med 297 1091 1977
4 Selzer A Use of anticoagulant agents in acute myocardial infarction Am J Cardiol 41 1315 19 8
5 Roberts, B Rosato F and Rosato E Heparin—A cause of arterial emboli? Surgery 55 803 1964
6. Weismann, R., and Tobin R Arterial embolism occurring during systemic heparin therapy Arch. Surg 76 219 1958
7 Ur A Fatal embolism despite heparin treatment Lancet 1 959 1976
8. Rhodes, G Dixon, R., and Silver D Heparin induced thrombocytopenia with thrombotic and hemorrhagic manifestations Surg Gynecol Obstet 136 409 1973
9 Bell W., Tomasulo P., Alving B and Duffy T Thrombocytopenia occurring during the administration of heparin Ann Intern Med 85 155 1976
10 Klein H and Bell, W Disseminated intravascular coagulation during heparin therapy Ann Intern Med 80 477 1974
11 Barker C Rosato F., and Roberts B Peripheral arterial emboli Surg Gynecol Obstet 22 123 1966
12 Sugiura M., Hiraoka K Ohkawa S Ueda K., Matsuda T., and Murakami M A clinicopathological study on cardiac lesions in 64 cases of DIC Jpn Heart J 18 57 197
13 Jenkins, J and Keep P Fatal embolism despite low dose heparin Lancet 1 541 1976
14 Maseri A, L'Abbate A., Baroldi G., Chierchia S., Marzilli, M Ballestra A. Severi, S., Parodi, O Biagini, A. Distante A and Pesola A. Coronary vasospasm as a possible cause of myocardial infarction N Engl J Med 299 1271 1978
15 Maseri A Severi S Nes M L'Abbate A Chierchia S Marzilli M *Ballestra* A., Parodi, O Biagini A and Distante A Variant angina One aspect of a continuous spectrum of vasospastic myocardial ischemia Am J Cardiol 42 1019 19 8

Clinical pathologic conference

Michael L Epstein M D
Augustin G Formanek M D
F Blanton Bessinger M D
Jesse E Edwards M D
St Paul Minn

DR EPSTEIN A male infant with a birth weight of 3 380 grams was referred to the University of Minnesota Hospitals at one day of age because of cyanosis that was unresponsive to supplemental oxygen administration Clinical examination revealed a right sided cardiac impulse and a Grade 3/6 systolic diastolic murmur along the right cardiac border The second sound was loud and single The lower edge of the liver was palpable 3 cm below the left costal margin

The apgar scores were 6 and 9 Arterial blood gases with the patient inspiring 80 per cent oxygen showed a pH of 7 33 with a pCO of 46 torr and a pO of 35 torr Results of other laboratory data included normal serum electrolytes calcium creatinine blood urea nitrogen complete blood count and liver function tests Occasional Howell Jolly bodies were present on an initial blood smear although a liver-spleen scan demonstrated the presence of a spleen

An echocardiogram demonstrated two atrioventricular valves and a single large anterior great vessel not in continuity with either atrioventricular valve A ventricular septum was not definitely identified

The electrocardiogram demonstrated a mean frontal plane P axis of +150 degrees with a mean frontal plane QRS axis of −90 degrees (Fig 1) A PR interval of 0 16 sec prolonged for a patient of this age was recorded Although far right chest leads were not obtained the available leads demonstrated probable right ventricular hyp trophy

Dr Formanek will you present the roentge graphic findings?

DR FORMANEK The posteroanterior thora roentgenogram shows decreased pulmonary v culature The aortic arch and the descend aorta are very likely on the left side The gast bubble and the apex of the heart rate on the r side The shadow of the liver is on the left (Fig 2) These findings indicate either (1) abdo inal heterotaxia with situs indeterminus or complete situs inversus with left aortic arch a left descending aorta

Ventriculography in frontal and lateral proj tions was performed (Fig 3) The catheter w advanced through a left sided inferior vena ca into a large ventricle situated anteriorly infundibular chamber is present from which t aorta arises anteriorly There is a left aortic ar with left descending aorta A posteriorly loca small pulmonary artery is opacified through a k ductus arteriosus The main pulmonary artery well visualized and is markedly hypoplastic in most proximal portion

From the inferior vena cava the cathete w advanced, very likely through an interatri communication into the superior vena ca which is on the right side Injection was made this superior vena cava (Fig 4) This resulted dense opacification of an atrium with ro shape and atrial appendage which is located the right of the superior vena cava and is po anteriorly The shape and course of the atri appendage indicates an anatomical left atri There is faint opacification of another atrium well There is dense opacification of the sa ventricle as seen in Fig 3 but the source of g into this ventricle is uncertain

From the Departm [illegible] Radiology and Pathology University of M[illegible] and the Department of Pathology United H[illegible] St Paul Minnesota

This study was supp[illegible] Health Service Research Grant 5 R0[illegible] from the National Heart, Lung [illegible]

Recei ed for publication [illegible]

Reprint requests Jesse E E[illegible] United Hospitals-Miller Di[illegible] St Paul Minn 5510?

000? 8703/80 040 10 + 07500/0 © 1980 The C V Mo[illegible]

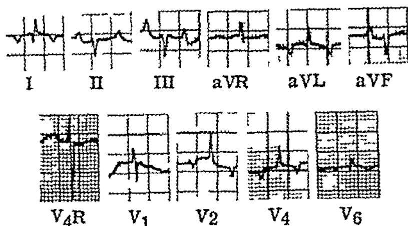


Fig 1 Electrocardiogram

In this case the situs was very difficult to determine because in situs inversus with left aortic arch the descending aorta should cross the midline in the lower thorax and be located in the abdomen to the right of the spine Unfortunately the abdominal aorta was not clearly seen in the frontal projection of the angiocardiogram Similarly in situs inversus the superior vena cava should be on the left rather than on the right side this is not the case here (Fig 4a) On the basis of the films that are available it is very likely that this patient has a situs indeterminus (abdominal heterotaxia) with dextroversion of the heart The congenital anomaly as judged by angiography is compatible with single ventricle with transposition of the great vessels and atresia of the pulmonary artery There is a patent left ductus arteriosus Two atria are present with very likely the right superior vena cava entering directly into a right sided anatomic left atrium

Dr Epstein Thank you Dr Formanek During cardiac catheterization the following facts were elicited

There was a persistent right superior vena cava draining into the right sided atrium Pulmonary atresia was discovered with pulmonary blood flow depending on a patent ductus arteriosus The patient underwent a right subclavian to pulmonary artery anastomosis (Blalock Taussig shunt) The postoperative course was uncomplicated

The infant again presented to the University of Minnesota Hospitals at about 4 months of age with a 2 to 3 week history of irritability and mild symptoms of upper respiratory disease He suffered a sudden hypotensive cardiorespiratory arrest and died shortly after readmission



Fig 2 Frontal view of thoracic roentgenogram

Dr Bessinger will you present the differential diagnosis?

Dr Bessinger This case presents a common problem to the cardiologist seeing neonates namely persistent cyanosis There is the interesting finding of dextrocardia in association with apparent situs inversus The infant was of normal size following an unremarkable pregnancy therefore diseases affecting the premature infant do not immediately come to mind The key fact in the presentation is the persistence of generalized cyanosis that was unresponsive to high FiO_2 as evidenced by the pO_2 of 35 torr while inspiring 80 per cent oxygen The other key fact is the chest x ray which showed the cardiac silhouette to be enlarged and the pulmonary vascularity to be

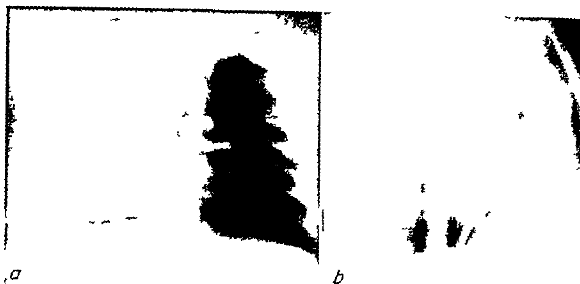


Fig 3 Ventriculography after the catheter had passed into the heart through a left sided inferior vena cava a Frontal view b Lateral view



Fig 4 Angiocardiograms made after passing the catheter through the left sided inferior vena cava then through the atrial portion of the heart and into a right sided superior vena cava Injection made into latter a Frontal view b Lateral view

decreased This combination of persistent arterial hypoxemia in spite of increased FIO and decreased pulmonary vasculature leads one to a consideration of congenital cardiac lesions that cause obstruction to pulmonary blood flow with right to left shunting These lesions are compatible with intrauterine circulation but become very obvious once the infant is delivered and is dependent upon his own pulmonary blood flow for adequate arterial oxygenation In this group are Ebstein s anomaly tricuspid atresia and pulmonary atresia (or severe pulmonary stenosis) ei

ther with intact ventricular septum or wi tricular septal defect The cardiac exami showed findings that are compatible in th first heart sound was normal and the heart sound was increased and single This finding suggests the absence of one sem valve and perhaps anterior displacement aorta The 3/6 cardiac murmur was comp with a patent ductus arteriosus and interest was heard best along the right sternal borde physical examination suggested the "wrink this case in that the liver was palpable on th

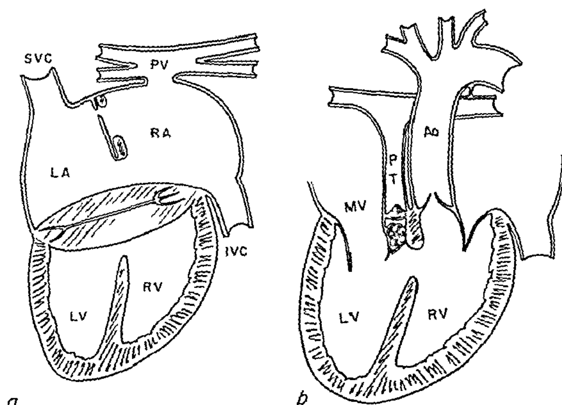


Fig. 5. Essentials of the intracardiac structures. *a*, Detailing the atrial connections and ventricles. The anatomic right atrium (*RA*) lies on the left side and receives the pulmonary veins (*PV*). The anatomic left atrium (*LA*) lies on the right side and receives a right sided superior vena cava (*SVC*). There is a large atrial septal defect in the lowermost part of the atrial septum beneath which is a common atrioventricular valve. Beneath the latter is an interventricular communication. The inferior vena cava (*IVC*) lies on the left and joins the anatomic right atrium. The ventricles are inverted. The anatomic right ventricle (*RV*) lies on the left and the anatomic left ventricle (*LV*) lies on the right. *b*, Details of the ventricular connections. The inverted right ventricle (*RV*) leads to a transposed aorta (*Ao*), while the pulmonary trunk (*PT*) arises from the inverted left ventricle (*LV*). The pulmonary valve is atretic and the subpulmonary zone is obstructed by accessory endocardial tissue. *MV* = inverted mitral valve.

side and the cardiac impulse was palpable over the right chest. Thus, from the physical examination, the chest x ray, and the persistent cyanosis one is led to the fact that the child is ductus dependent and therefore has some type of congenital lesion resulting in severe or total obstruction to pulmonary blood flow from the heart.

In considering the chest x ray, the finding is that of complete situs inversus. While patients may have complete situs inversus of thoracic and abdominal viscera and have completely normal hearts, the incidence of cardiac disease has been estimated to be increased to 3 to 9 per cent, and in those with cardiac disease 80 per cent have been reported as having the cyanotic type of congenital disease. The chest x ray findings do not suggest the situation where situs is indeterminate, as in the asplenia and polysplenia syndromes. The x ray findings of an enlarged heart in association with decreased vascularity suggests Ebstein's anomaly, tricuspid atresia, or pulmonary atresia with intact septum as opposed to the more usual picture of normal cardiac size in pulmonary atresia with ventricular septal defect (tetralogy of Fallot).

The electrocardiogram is interesting in that the P wave axis is toward the right and inferior, compatible with a situs inversus of the atria. The frontal plane QRS axis of minus 90 degrees is interesting. If the patient had situs solitus and an axis of minus 90 degrees, endocardial cushion defect would come immediately to mind. The chest leads did not include complete right chest leads. A diagnosis of right ventricular hypertrophy on the electrocardiogram would be helpful in that it would be evidence against an Ebstein's anomaly or tricuspid atresia. On the other hand, the presence of right atrial enlargement on the



Fig 6 *a* Anterior view of thoracic organs The apex of the heart points toward the right and the aorta (*A*) is the more anterior of the two vessels Each lung has three lobes (*U* = upper *M* = middle *L* = lower) *LAD* = left anterior descending coronary artery *b* Posterior view of thoracic organs showing confluence of pulmonary veins (*PVC*) from which through an orifice (*probe*) the confluence of pulmonary veins leads into the left sided anatomic right atrium (*RA*) *LA* = right sided anatomic left atrium *c* Left-sided anatomic right ventricle (*RV*) leading to the aorta (*A*) *d* The right sided anatomic left ventricle (*LV*) and pulmonary trunk (*PT*) The pulmonary valve (*V*) is atretic and dome shaped while beneath the valve is accessory tissue (*M*) which causes subpulmonary stenosis Inferior to this lies the mitral valve which is in fibrous continuity with the pulmonary valvular tissue

electrocardiogram would be compatible with each of these condition

In the report of Stanger and associates on necropsy specimen showing cardiac malpositions 13 cases had complete situs inversus In three the hearts were normal In the remaining ten cases there were various types of anomalies six having pulmonary stenosis (or pulmonary atresia) Interestingly one patient was reported as having a persistent common atrioventricular canal

The echocardiogram is of help in ruling out some of the general considerations Two atrioventricular valves were identified thereby elim-

ing tricuspid atresia as a consideration Only one great vessel was identified consequently pulmonary atresia is still strongly under consideration The lack of continuity between a great vessel and a posterior atrioventricular valve is bothersome No septum was seen and so one has to consider that the patient may have single ventricle with transposition of the great arteries and pulmonary atresia This is a more complex abnormality than the tetralogy of Fallot but still has the functional abnormality namely obstruction to pulmonary blood flow from the heart and dependency of the patient on the patency of the ductus arteriosus This dependency is supported by the clinical course of the child in that progressive hypoxemia and resultant metabolic acidosis occurred presumably secondary to progressive closure of the patent ductus arteriosus

The complex anomalies that are seen in the asplenia syndrome have received much attention in the literature These most commonly include pulmonary atresia transposition of the great arteries and total anomalous pulmonary venous connection In this particular case however the chest x ray does not show discordance between the stomach bubble and cardiac apex the tipoff to consideration of indeterminate situs and asplenia

In summary the case presents as an infant with persistent cyanosis The cardiac examination suggested that the infant has a patent ductus arteriosus for his pulmonary blood flow Laboratory tests support a diagnosis of pulmonary atresia in association with single ventricle and transposition of the great arteries

DR EPSTEIN Thank you Dr Bessinger I shall now describe the autopsy findings

At autopsy total situs inversus of both the thoracic and abdominal viscera was found A single normal appearing spleen was present in the right upper quadrant of the abdomen as was the stomach The essentials of the cardiac and vascular structural abnormalities are summarized in Fig 5

The cardiac apex was directed to the right The aorta arose anteriorly and to the left of the pulmonary trunk (Fig 6a) It ascended on the left and passed over the left bronchus The descending aorta remained on the left side The branches of the aortic arch from before backward were the innominate left common carotid and left subclavian arteries The previously performed right subclavian to right pulmonary artery anastomosis was identified The ductus arteriosus now represented by a ligamentum arteriosum ran between the aorta and left pulmonary artery

The inferior vena cava was left sided while the one superior vena cava was on the right

The anatomic right atrium was on the left side of the heart It received the inferior vena cava but not the superior vena cava No coronary sinus was present The left sided anatomic right atrium also received the entire pulmonary venous return by way of a wide opening from an accessory chamber lying slightly posteriorly and superiorly (Fig 6b) A large inferoposterior atrial septal defect allowed free communication between the left sided venous atrium and a smaller right sided anatomic left atrium The only venous connection with the right sided arterial atrium was the solitary right sided superior vena cava

Below the inferoposterior atrial septal defect was a common atrioventricular valve of the complete type (Fig 6c) Among the leaflets of this valve were common anterior and posterior leaflets each straddling a large deficiency of the ventricular septum Through this free interventricular communication occurred The configuration of the valvular tissue and the patterns of the tensor apparatus indicated that the left portion of the common atrioventricular valve was derived from the tricuspid component while the mitral component formed the right side of the common valve

Of the two ventricles the one that lay anterior and to the left was highly trabeculated and gave rise to an infundibulum and from the latter in turn arose the aorta (Fig 6c) The posterior ventricle positioned on the right side was smooth walled and somewhat dilated The outflow tract of the posterior ventricle was obstructed by accessory tissue which resembled atrioventricular valvular tissue (Fig 6d) This tissue arose from the anterior crest of the VSD and was directed posteriorly and superiorly making an attachment to the anterolateral wall of the right sided posterior ventricle

The pulmonary valve arose from the right sided posterior ventricle and was atretic The pulmonary valvular tissue was in fibrous continuity with the mitral portion of the anterior leaflet of the common atrioventricular valve (Fig 6d) The pulmonary trunk measured only 2 to 3 mm in diameter at the anulus but gradually widened until it branched into relatively right and left pulmonary arteries

Each lung was trilobed and on each side the broncho arterial relationships were those characteristic of the right lung (Fig 6a) All of the pulmonary veins drained into a common accessory atrium' which in turn, drained through an unobstructed opening into the left sided anatomical right atrium

The coronary arteries arose from the aorta The left coronary artery entered the left sided AV sulcus without branching A short distance from the aorta the right sided coronary artery divided into anterior descending and circumflex branches

Dr Edwards would you please comment on this case?

DR EDWARDS Several previously described anomalous complexes are brought together in this one case Included in these are (1) complete transposition in situs inversus [6] (2) the inverse of the developmental complex of (a) termination of the left superior vena cava in the left atrium (b) absence of the coronary sinus and (c) a posteroinferiorly lying atrial septal defect as described by Raghib and associates and (3) cor triatriatum terminating in the anatomic right atrium [8]

In the developmental complex described by Raghib and associates, some subjects showed the basic complex coupled with persistent common atrioventricular canal as in this case In this combination the atrial septal defects of each of the two conditions coalesce yielding a large defect that includes all of the lowermost part of the atrial septum

In the syndrome of Raghib there are two superior venae cavae The case here presented shows a deviation in that the left sided right superior vena cava was absent

With regard to the association of pulmonary stenosis or atresia in complete transposition a number of anatomic states may cause obstruction to pulmonary flow Two were shown by this case each uncommonly seen in complete transposition These were pulmonary valvular atresia and subvalvular accessory endocardial tissue

In general the features of total situs inversus (with associated malformations) were displayed by this case but two exceptions are notable The first of these was the presence of a left aortic arch without retroesophageal segment This is not a surprising feature and may be viewed as the inverse of the relatively mmon right aortic arch without retroesophageal egment as seen in the tetralogy of Fallot The other is the occurre bilateral right sidedness as far as the lun concerned This condition is classic for the a ic syndrome[9] and its occurrence in assoc with an existing spleen adds unanswered tions about the association of splenic with organ laterality

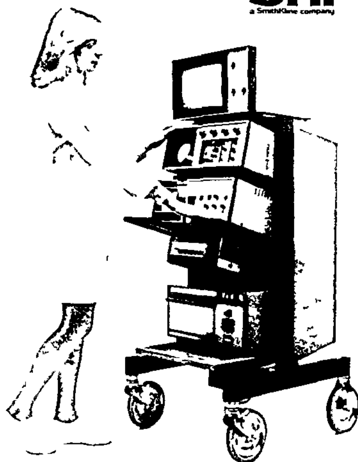
The combined effects of the anomalies upon the circulation is of interest to consi

If one views this case as an example of co transposition the fact that all of the pulm venous blood was carried into the lef venous atrium was a favorable additional a ly Similar is the fact that the solitary su vena cava joined the arterial atrium I presence of these 'venous crossings" the functional abnormality resides in the obstr to pulmonary arterial flow in association w interventricular communication

Final diagnoses Situs inversus with con transposition pulmonary atresia cor triatr leading to venous atrium persistent co atrioventricular canal and termination perior vena cava in arterial atrium with a coronary sinus

REFERENCES

1 Cockayne E A The genetics of transposition viscera Q J Med. 31 479 1938
2 Torgersen J Genic factors in visceral asymmetr the development and pathologic changes of lung and abdominal organs Arch Pathol 47 566 19
3 Lowe C R., and McKeown T An investiga dextrocardia with and without transposition of nal viscera with a report of a case in one more twin Ann Eugen 18 267 1954
4 Keith J D Rowe R D and Vlad P Heart D Infancy and Childhood, New York 1958 Ma Publishing Co Inc pp 538 54
5 Stanger P Rudolph A M and Edwards, J E malpositions An overview based on study of necropsy specimens Circulation 56 1 9 1977
6 Jue K L Adams P Jr Pryor R Blount and Edwards J E Complete transposition of th vessels in total situs inversus Anatomic electr graphic and radiologic observations Am J 17 389 1966
7 Raghib G., Ruttenberg H D Anderson P C A K Adams P Jr and Edwards J E Termina left superior vena cava in left atrium atrial sep and absence of coronary sinus A develop complex Circulation 31 906 196
8 Lam C R., Green E., and Drake E Diagno surgical correction of 2 types of triatrial heart, 51 127 1962
9 Soto B., Pacifico A. D., Souza A S Jr Barg M Jr Ermocilla R and Tonkin I L Identifi thoracic isomeri m from the plain chest radiogra J Roentgenol 131 995 19 8



American Heart Journal

Articles to appear in early issues

Necrotizing vasculitis coronary angiitis and the cardiologist
Joseph E Parrillo M D and Anthony S Fauci M D Bethesda Md

Correlation of the location of coronary arterial spasm with the lead distribution of ST segment elevation during variant angina
Rex N MacAlpin M D Los Angeles Calif

Prognostic significance of an ST segment depression of patients with an acute coronary attack
H Raunio V Rissanen S Rehnberg Y Jolinen M Helin and K Pyorala Kuopio Finland

Low dose heparin in the prevention of deep vein thromboses in patients with acute myocardial infarction
Aubrey Pitt M D F R A C P Stanley T Anderson F R A C P Peter C Habersberger F R A C P and David S Rosengarten F R A C S Melbourne Australia

Captopril in severe treatment resistant hypertension
Roger K Ferguson M D Peter H Vlasses Pharm D Janice R Koplin B S Anne Shirinian B S James F Burke Jr M D and John C Alexander M D Philadelphia Pa

The role of echocardiography in the selection of mitral valve prostheses
Charles E Denbow M D James R Iluth M D and Emilio R Giuliani M D Rochester Minn

Comparison of antiarrhythmic effects of oral prajmalium bitartrate and intravenous lidocaine in acute myocardial infarction
Wulf Dirk Bussmann M D Sybille Schreiber and Martin Kaltenbach M D Frankfurt W Germany

The rhythm of the heart in active elderly subjects
A John Camm M B M R C P K E Evans M R C S D F Ward M B M R C P and Anthony Martin M D Crawley W Sussex and London England

Serum chromium in patients with recent and old myocardial infarction
Abraham S Abraham M D Moshe Sonnenblick M D Maya Eini Ovadiah Shemesh M D and Ahron P Batt Jerusalem Israel

Recurrent angina after bypass surgery evaluation by early and late arteriography
Robert I Hamby M D Irwin Hoffman M D Daniel Weiss M D Julius Ganz M D and J B George Wisoff M D New Hyde Park Jamaica and Stony Brook N Y

The effect of allopurinol on the degree of early myocardial ischemia
William L Arnold M S Richard A DeWall M D Paul Kezdi M D and Hans H J Zwart M D Dayton Ohio

Sudden death in cardiomyopathy role of bradycardia dependent repolarization changes
J e K Bissett M D John W Watson M D James A Scott M D Neil de S a M D and David W Ohrt M D Little Rock Ark

Instrumental methods in the study of vascular disease

Jerrold S Lieberman M D
New York N Y

Instrumental methods for assessing blood flow in the extremities facilitate the physiological approach to diseases of the peripheral circulation An extensive clinical experience has developed using noninvasive techniques which are easily available to the clinician and basic determinations can be done at the bedside The physician s history and physical examination remain the cornerstone of patient care but during the past decade laboratory testing has become an integral part of the clinical evaluation In arterial occlusive disease these studies enable accurate diagnosis precise localization and quantification of the functional impairment In venous thromboembolism they offer reliable screening tests and often an alternative to venography In vasospastic disease they provide quantitative objective physiological evaluation This review will describe the contribution of noninvasive testing and the vascular laboratory to the diagnosis and management of vascular diseases

Physiological considerations

In arterial occlusive disease (AOD) the major hemodynamic determinants of blood flow are the diameter of the stenosis and the velocity of blood flow (Fig 1A) Arterial stenoses and the terminal vascular bed are analogous to electrical resistances in series and stenosis becomes significant when its resistance becomes comparable to that of the the distal vascular bed Reduction of the diameter of the arterial lumen has little effect until a large percentage of the cross sectional area has been obliterated and a critical stenosis has been reached Blood flow then falls off rapidly and progressively with a corresponding increase in the pressure drop across the stenosis (Fig 1B)

When velocity increases critical stenosis is reached at a lesser degree of narrowing and a previously non significant stenosis will produce hemodynamic abnormalities even though resting flow had been normal Following exercise or a period of circulatory arrest by a tourniquet calf blood flow in normal limbs will increase promptly up to 20 times the resting rate However stenosis of the inflow artery as in AOD will delay the time of peak flow reduce the absolute value of peak flow and prolong the recovery time (Fig 2) When the systolic pressure is measured at the ankle AOD will reduce the pressure and prolong the recovery time The initial drop is an index of main artery stenosis and the increase in recovery time reflects the total flow deficit The hemodynamic and pathophysiologic aspects of vascular diseases have been reviewed by Strandness and Sumner

In clinical terms an atherosclerotic plaque will have little effect on blood flow until it has occluded a major portion of the arterial lumen The inverse relationship between flow volume and pressure drop across a stenosis enables the physician to use the simple noninvasive indirect measurement of pressure to provide quantitative information on blood flow in the extremities and diagnostic maneuvers utilizing limb exercise or circulatory arrest will increase the sensitivity of

From Cornell University Medical College and the Vascular Section The New York Hospital New York N Y

Supported in part by the Sidney Prince Trust

Received for publication Aug 1 1979

Reprint requests Jerrold S Lieberman M D Dept of Medicine The New York Hospital Cornell Medical Center Division of Cardiology 525 E 68th St New York N Y 10021

Clinical Associate Professor of Medicine Cornell University Medical College and Associate Attending Physician and Physician-in-Charge Vascular Section The New York Hospital

0002 8703/80/010 1 + 11$01 10/0 © 1980 The C V Mosby Co

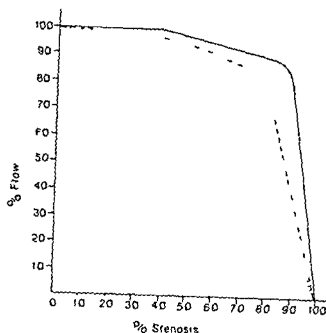


Fig 1A Arterial stenosis has little effect on blood flow until critical stenosis is reached it then causes a rapid and progressive decrease in blood flow As flow velocity increases critical steno is is reached at lesser degrees of stenosis and in this instance the resting flo v rate at 80% stenosis *(solid line)* would show no significant abnormalities but if flow velocity were increased by exercise or reactive hyperemia as in *the dashed* and then *dotted curves* the reduction in flow would become significant

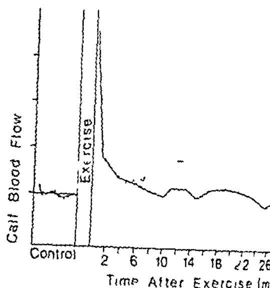


Fig 2 In a normal limb post exercise hyper mia (sol is characterized by prompt sharp peak flow and rapid to control level In a markedly ischemic limb (inter line) there is marked delay to peak time and prolongat the recovery time

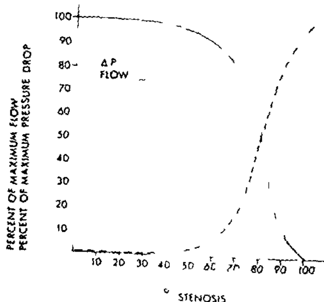


Fig 1B The pres ure drop acr ss the st nosis is inversely proportional to the re ... and rises sharply as flow decreases The in ... ment of systolic blood pressure ... ment in the vascular laboratory

the testing by increasing the velocity of bl flow

The pathophysiology of arterial insufficienc demonstrated in intermittent claudication In normal limb walking will cause a ten to twen fold increase in calf blood flow but when ther proximal arterial stenosis the initial increase flow will cause the stenosis to become critic The increased pressure drop will decrease d arterial pressure until intra arterial pres within the calf muscle falls below the surround tissue pressure at this time flow through t muscle bed will fall dramatically or cease a characteristic ischemic pain will appear Wh the patient halts muscle contractions cease ar in the recovery phase pain continues until th metabolic debt has been repaid During the recov ery phase the hyperemic flow through the re muscle creates a shunt which steals from th ankle and increases the drop in ankle blood pressure Since walking distance is related to stenosis of the large arteries and al o to the work load it is predictably influenced by the speed of walking or by grades

On physical examination the normal nutriti al state of the feet will attest to the normal resting blood flow in early claudication I advanced disease trophic skin changes how tha stenosis is critical even at resting flow rates

Pallor in elevation is indicative of large artery involvement with reduced pressure while dependent rubor indicates dilation of the capillary bed in response to ischemia and reduction in total blood flow. In patients with early stenosis or segmental occlusion with good collaterals the pulse may be palpable at rest but disappear with exercise.

The venous bed is easily distensible and flow is low and not pulsatile. As a result physical examination is notoriously unreliable in the estimation of venous flow and in the recognition of thrombophlebitis, which is a venous occlusive disease. In the hand skin color provides an enjoyable and direct demonstration of blood flow. In the Allen test the rate of flow into the hand is directly visualized when the physician releases his pressure at the patient's wrist. Hang ups indicate occlusion of the smaller arteries and the duration of the hyperemic flush gives a measurable recovery time.

Instrumentation

Plethysmography is the measurement of changes in the volume of an organ or limb and is the reference standard for the measure of blood flow in the extremities. The original technique was cumbersome and time consuming but newer pneumatic plethysmographs utilize simple cuffs for the calf studies and plastic cups for toes and fingers. Electronic transducers provide an analog readout.

Indirect methods have further enhanced the flexibility and availability of the plethysmographic technique. The mercury strain gauge (MSG) is a slender elastic tube filled with mercury which encircles the limb or digit. Changes in the circumference and volume of the limb segment enclosed by the gauge will generate an analog signal which is linearly related to the volume changes. Simple "black boxes" are commercially available in which a closed loop gauge is slipped over the tip of a finger or a toe. These units, which are usually not calibrated, attach directly to the office electrocardiogram to give pulse wave traces at the bedside. Calibration can be done off the limb with a micrometer.

In impedance plethysmography (IMP) two electrodes are applied directly to the limb and when a high frequency low current signal is passed between them the changes in blood volume between the electrodes will generate voltage changes proportional to blood flow. When four electrodes are used this method can be calibrated in accurate percentage changes but absolute values cannot be obtained. IMP is widely used for venous outflow studies.[1]

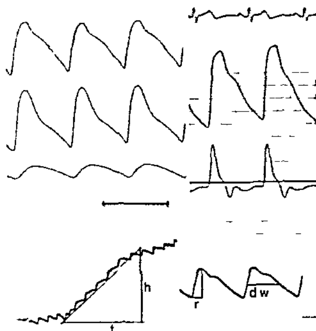


Fig 3 Plethysmography. *Upper left* Simultaneous, standardized digital pulse wave forms as recorded with a pneumatic plethysmograph (Windsor). From above: a normal finger, a normal toe and a toe distal to a low grade femoral popliteal occlusion. Time marker is 1 second. *Upper right* A normal toe pulsation as recorded with mercury strain gauge. The first derivative is recorded below and resembles the velocity curve or the Doppler signal. *Lower left* Finger blood flow by venous occlusion plethysmography. With calibration h/t represents the blood flow/unit of time/volume of tissue. *Lower right* Rise time *(r)*, width at half amplitude *(dw)* when expressed as percentage of cycle length are easily obtained and enable simple quantification.

Any of the plethysmographic methods can be used to determine systolic blood pressure (SBP), to record digital pulse wave forms or to evaluate arterial or venous flow by venous occlusion (Fig 3). For SBP the plethysmograph is used as a pulse detector corresponding to the stethoscope in the auscultatory technique. It will give accurate measure of the systolic pressure at the site of the cuff regardless of where the distal sensor is positioned. However the diastolic pressure cannot be obtained.

Digital pulse wave forms lend themselves easily

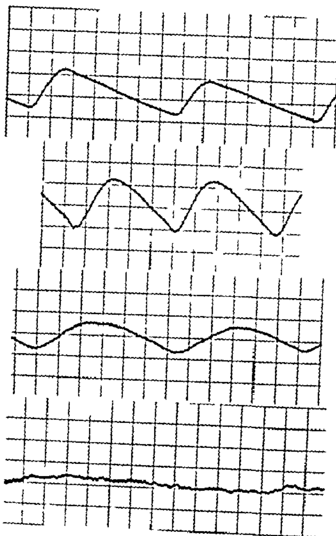


Fig 4 [illegible] with the mercury strain gauge *The* [illegible] is normal as the dicrotic notch does not [illegible] normal [illegible] With progressive arterial [illegible] the [illegible] of the ascending limb [illegible] the peak time [illegible] delayed and the downstroke [illegible] the umbrella curve *in* [illegible] *trap* flow is no longer [illegible] arterial insufficiency

to [illegible] For quantitation the simple time intervals of rise time and pulse width at half amplitude have been described (Fig 3) With the calibrated instruments absolute pulse dimensions [illegible] The plethysmographic signal [illegible] differentiated electronically and the first [illegible] resembles the velocity wave form in the [illegible] has described sophisticated method [illegible] form analysis

Quantitative [illegible] arterial blood flow is accomplished by [illegible] plethysmography with pneumatic [illegible] gauge techniques A cuff is applied proximal [illegible] the part that is to be studied and after calibration and base

line stabilization the cuff is rapidly infl[illegible] subdiastolic pressure usually 40 to 60 [illegible] Initially only venous outflow is bloc[illegible] arterial blood will distend the vasuclar [illegible] the venous pressure reaches occluding [illegible] sure The slope of this volume tracing re[illegible] arterial blood flow (Fig 3) For acute stu[illegible] amplitude of the digital pulse wave is [illegible] function of blood flow to the digit and [illegible] accurate index of changes in blood flow [illegible] measurement cannot be calibrated and o[illegible] centage changes can be obtained Norma[illegible] pulse wave forms have a rapid systolic ups[illegible] sharp peak early in the cycle and a d[illegible] downstroke with upward concavity A [illegible] notch is usually present in the fingers but [illegible] toes Distal to a stenosis the plethysmo[illegible] curve loses its characteristic shape and un[illegible] progressive loss of amplitude and deteriora[illegible] form to an umbrella shape to a straig[illegible] (Fig 4)

In venous studies peak venous outflow [illegible] sured by positioning the plethysmograph[illegible] on the calf A collecting cuff above the k[illegible] inflated to a venous collecting pressure an[illegible] rapidly deflated while the volume chan[illegible] recorded (Fig 5)

The Doppler Flowmeter (DFM) deter[illegible] blood velocity by a noninvasive transcuta[illegible] method Two piezoelectric crystals are mo[illegible] in a hand held probe which is placed ove[illegible] artery or vein and contact is made throu[illegible] acoustic gel The transmitting crystal is ene[illegible] to emit an ultrasonic beam at a frequen[illegible] between 2 and 10 MHz and when a small per[illegible] age of the beam is reflected back by the m[illegible] red cells within the vessel the frequency of [illegible] signal is altered in accordance with the fa[illegible] Doppler shift The reflected sound waves ge[illegible] ate a small electrical signal in the rece[illegible] crystal the emitted and received signal [illegible] compared electronically and the instrument [illegible] erates an audible signal whose frequency is [illegible] portional to flow velocity—a higher pitch re[illegible] senting a greater velocity With DFM ausc[illegible] tion of the audio signal represents a subject[illegible] form of wave form analysis and the nor[illegible] arterial signal can be recognized by the [illegible] triphasic configuration Distal to a [illegible] occlusion the signal will be low pitched and [illegible] monophasic These signals can also be rec[illegible] graphically (Fig 6) Quantitative velocity [illegible]

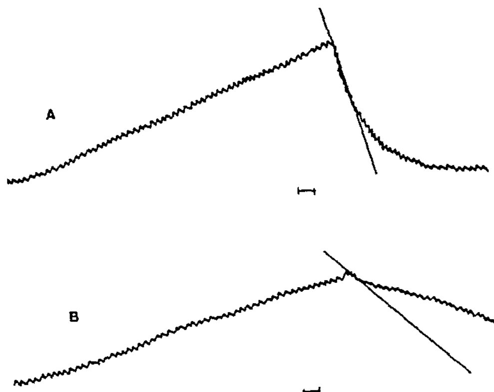


Fig 5 Impedance plethysmography for venous outflow in a normal limb *(A)* and with deep vein thrombosis *(B)* Th maximum venous outflow (MVO) is drawn by in pection and is reduced in the lower tracing

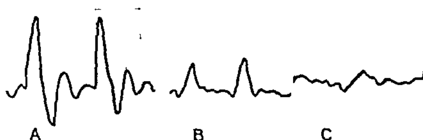


Fig 6 Arterial signals with the Doppler flow meter analog recording *A* The normal signal is made triphasic by the reverse flow in early dia tole with subsequent forward flow *B* With early stenosis peak flow is lower and there i los of diastolic reverse flow *C* With severe stenosis the rate of flow is markedly reduced the pitch is lower and the signal is highly damped

surements and the analysis of slopes areas and time intervals have been used to generate sophisticated flow indices including the pulsatility index damping factor transit time and turbulence factor [4] Spectral analysis requires further instrumentation and will display the distribution of multiple velocities in real time

Because of its availability and the ease with which it can be used DFM has become a first line instrument widely used in clinical practice The audio signal provides a simple accurate pulse detector for the determination of segmental systolic blood pressures and can be interpreted by auscultation In daily practice the instrument may become part of the physician s routine vascular examination much like the ophthalmo

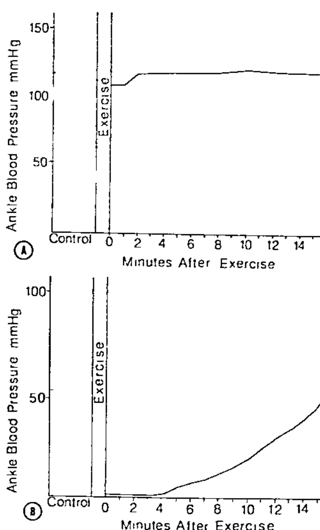


Fig 7 Ankle blood pressure response to treadmill exercise *A* There is no ignificant change in AP in the normal limb after 5 minutes of treadmill exercise *B* With moderate arterial insufficiency the control blood pressure is lower than the brachial, AP falls after exercise and recovery is delayed

scope or stethoscope As a detector of venous blood flow the instrument enables bedside eluci dation of venous hemodynamics for the detection of deep vein thrombosis Pocket size and small portable instruments are available commercially The smaller audio units and the less sophisticated analog devices determine the presence and rela tive velocity of flow but not the direction They are adequate for most clinical studies and the directional information is more likely to be required for quantitative studies or physiological investigation DFM is extremely sensitive and signals may be obtained from small arteries Detection of a flow signal is not necessarily equivalent to palpation of an arterial pulse on physical examination

High technology imaging techniqu intermittent ultrasound pulses rather tinuous waves They enable the display sectional areas in real time and Dop profiles at specific sites within the vess noninvasive techniques Radioisotope studies use washout techniques to meas flow in skin and muscle They have not extensively in the clinical vascular labo

Arterial occlusive disease

The laboratory evaluation of AOD ut noninvasive indirect determination of provide information on blood flow in ac with the relationships shown in Fig 2 measurement is the ankle arm pressure and additional information is obtained tolic pressures at other levels the re exercise or reactive hyperemia and w analysis [17, 24]

For ankle systolic blood pressure (AP) is applied to the lower leg just above the If DFM is used the probe is held posterior tibial or dorsalis pedis artery ar heard as with a stethoscope in plethy phy the sensor is applied to a toe appearance of pulsatile flow is observ strip chart recorder In normal subjects age AP will be about 15 mm Hg higher brachial A gradient is said to exist w ankle pressure falls below the brachial cates hemodynamically significant arteri sis or occlusion and its magnitude corr roughly to the degree of arterial insuf The gradient is often expressed as the index (PI) by dividing AP by the brachial pressure It will be unity or greater in limbs and a PI less than 1 is indicative As PI decreases it indicates greater redu blood flow with a single stenosis PI will be between 0 5 and 1 but multiple impose greater restriction on arterial flow will be below 0 5

Segmental systolic blood pressures further information Measurements may b high on the thigh above and below the k the ankle and on individual toes These m ments enable accurate localization of ind lesions and evaluation of their hemod significance Even with a special cuff thig sure may be artifactually elevated by as m 30 mm but other pressures approxima

temic in the normal limb and a pressure drop of 30 mm between two successive stations indicates a hemodynamically significant lesion

For wave form analysis quantitative plethysmographic tracings can be obtained at the same levels as the systolic blood pressures and have been utilized in the Pulse Volume Recorder (PVR) [1] Doppler wave form analysis provides corresponding information and has been utilized in the evaluation of aortoiliac disease [1]

As examples of clinical application a PI of less than 55 suggests that an ischemic ulcer is unlikely to heal without reconstructive surgery and when SBP toe falls below 30 mm there is high likelihood that gangrene will appear In a study of below knee amputations Barnes and colleagues found that when SBP below knee was greater than 70 mm Hg operative sites healed well but that when the pressure was below 50 mm Hg there was a significant risk of non healing

Ankle pressure gradients may fail to detect early stenosis or may be equivocal Exercise testing is helpful in this instance and will also provide better evaluation of total limb flow Exercise testing has been performed largely on the treadmill with Doppler determinations of AP The procedure is not standardized for speed and grade but the exercise is usually continued for five minutes unless claudication appears sooner AP is determined immediately after the exercise and at one minute intervals until the pressure returns to the control level to determine the initial pressure drop and the recovery time A pedal ergograph may also be utilized and Carter has used simple ankle flexion against the examiner s hand In our laboratory we have found 15 toe stands in 30 seconds to be a satisfactory exercise load and Hummel and associates reports that 30 toe stands are equivalent to the usual exercise test With these work loads normal subjects will maintain AP at control levels or show a brief drop of less than 15 mm Hg With arterial insufficiency the pressure will fall at least 20 mm or 20% from baseline and the recovery time may be from 4 to over 15 minutes The initial drop reflects the degree of occlusion of the main arteries while the recovery time measures total limb flow including collaterals The patterns of response can differentiate single from multiple occlusions (Fig 7)

Exercise tests require space equipment and the patient s cooperation They are time consuming when arterial insufficiency is severe and the

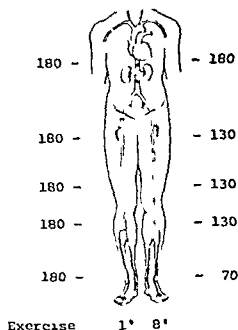




Fig 8 A vascular laboratory study The right leg is normal On the left the segmental systolic blood pressures indicate stenosis or occlusion of the left iliac artery and of the calf vessels distal to the popliteal The digital wave form recovery time and pressure index of 0 40 indicate moderate arterial insufficiency

workload makes it advisable that resuscitation procedures be available For these reasons the exercise load may be replaced by a period of circulatory arrest thus measuring post occlusive reactive hyperemia (PORH) A thigh cuff is inflated to an occluding pressure for 3 to 5 minutes and on its release reactive hyperemia will occur with an accelerated time scale Hummel and co workers[1] reported good correlation between PORH and treadmill exercise with a reduction in observation times from 20 minutes to 2 minutes AP was recorded at 15 second intervals Fronek and associates[13] occlude the arterial inflow for 4 minutes and measure PORH by observing increased velocity at the femoral artery with a Doppler probe They use the MSG simultaneously to follow the disappearance and subsequent return of pulsation in the toe [1]

In our own laboratory the basic arterial study

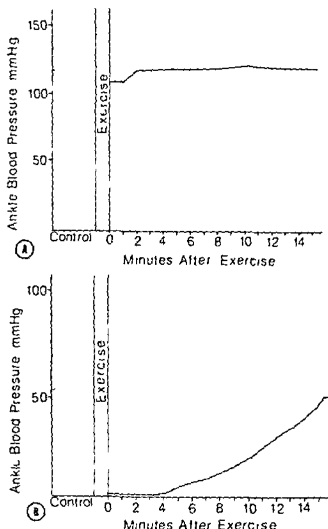


Fig 7 Ankle blood pressure response to treadmill exercise *A* There is no significant change in AP in the normal limb after 5 minutes of treadmill exercise *B* With moderate arterial insufficiency the control blood pressure is lower than the brachial AP falls after exercise and recovery is delayed

scope or stethoscope As a detector of venous blood flow the instrument enables bedside elucidation of venous hemodynamics for the detection of deep vein thrombosis Pocket size and small portable instruments are available commercially The smaller audio units and the less sophisticated analog devices determine the presence and relative velocity of flow but not the direction They are adequate for most clinical studies and the directional information is more likely to be required for quantitative studies or physiological investigation DFM is extremely sensitive and signals may be obtained from small arteries Detection of a flow signal is not necessarily equivalent to palpation of an arterial pulse on physical examination

High technology imaging techniques ut intermittent ultrasound pulses rather than c tinuous waves They enable the display of cr sectional areas in real time and Doppler f profiles at specific sites within the vessel all noninvasive techniques Radioisotope clear studies use washout techniques to measure bl flow in skin and muscle They have not bee u extensively in the clinical vascular laborator

Arterial occlusive disease

The laboratory evaluation of AOD utilizes noninvasive indirect determination of SBP provide information on blood flow in accorda with the relationships shown in Fig 2 The b measurement is the ankle arm pressure gradi and additional information is obtained from tolic pressures at other levels the response exercise or reactive hyperemia and wa e f analysis [17, 24]

For ankle systolic blood pressure (AP) the is applied to the lower leg just above the malle If DFM is used the probe is held ove posterior tibial or dorsalis pedis artery and fl heard as with a stethoscope in plethysmo phy the sensor is applied to a toe and appearance of pulsatile flow is observed o strip chart recorder In normal subjects the a age AP will be about 15 mm Hg higher than brachial A gradient is said to exist when ankle pressure falls below the brachial it i cates hemodynamically significant arterial ste sis or occlusion and its magnitude corresp roughly to the degree of arterial insuffic The gradient is often expressed as the pres index (PI) by dividing AP by the brachial syst pressure It will be unity or greater in n r limbs and a PI less than 1 is indicative of AC As PI decreases it indicates greater reduction blood flow with a single stenosis PI will u be between 0 5 and 1 but multiple sten impose greater restriction on arterial flow and will be below 0 5

Segmental systolic blood pressures prov further information Measurements may be m high on the thigh above and below the knee the ankle and on individual toes These measu ments enable accurate localization of indivi lesions and evaluation of their hemodyna significance Even with a special cuff thigh p sure may be artifactually elevated by as much 30 mm but other pressures approximate r

epetitive compression of the foot or lower calf nd readout by a six channel strip chart recorder ives information on the propagation of respirato y waves through the limb and the volume esponses to compression This instrument en bles a sophisticated semiautomated examina ion of the venous system but requires formal raining for both the technician and the interpret ing physician An accuracy of greater than 95% has been reported but confirmation by other laboratories has not yet been established

In the *radio fibrinogen uptake test* I labeled fibrinogen is administered intravenously and the legs are then scanned at intervals of one or more days with a hand held scintillation detector and rate meter When the count at one location remains significantly elevated for 24 hours the hot spot indicates that labeled fibrinogen is being incorporated into newly forming thrombus usually indicating the initial formation of thrombus within the venous arcades of the soleus muscle and the smaller veins of the calf Only half of these patients will have clinical signs of phlebitis and of all patients with abnormal uptake approximately 20% will extend into the popliteal femoral and iliac veins The test is limited by inability to detect thrombi in the pelvis or groin and a high false positive rate in the presence of trauma infection local surgery or bleeding It lacks precise localization of the extent of the thrombus and may not become positive until 72 hours after the isotope has been injected The test has been used extensively for prospective screening and provided the technological support for the recent studies of post surgical deep vein thrombosis and prophylaxis with low dose heparin

When used for clinical diagnosis the test is usually combined with a hemodynamic method as the false positive rate may reach 30% Because it indicates the active incorporation of fibrinogen into the clot it has been used to evaluate the recurrence of deep vein thrombosis in patients with post phlebitic edema who develop fresh symptoms but there are divergent reports on its reliability

Clinical application

The clinical diagnosis of DVT has an accuracy of approximately 50% and it is therefore advisable to confirm the diagnosis by at least one method before committing the patient to a full course of anticoagulation The initial testing may be done by Doppler ultrasound or by plethysmography according to the experience and facilities of the physician or hospital Either method is suitable and when the two are combined correlation with the venogram may reach 95% Fibrinogen uptake testing is sometimes combined with impedance plethysmography The role of phleborheography has not yet been established

When the vascular tests are abnormal and the totality of history physical examination and test results is sufficient in the physician s judgment to support the diagnosis of DVT anticoagulants may be given When the tests are equivocal or if another etiology such as extraluminal compression of the vein by pelvic tumor is suspected then the venogram becomes necessary When the tests are normal but clinical suspicion is high there may remain the possibility that thrombi are present in the deep femoral or calf veins or that non occlusive thrombi are present in the popliteal or more proximal veins This problem should also be resolved by contrast venography When there are relative contraindications to anticoagulation and the venogram shows clots confined to smaller veins of the calf the physician may elect to withhold anticoagulants and to monitor the patient with periodic noninvasive testing If subsequent tests show extension into the proximal veins the then documented risk of pulmonary embolism can be weighed against the hazards of anticoagulation for the individual patient

In the evaluation of other venous disorders ultrasound and plethysmographic studies are effective in differentiating lymphedema from post phlebitic edema and from deep vein thrombosis The role of hemodynamic studies in the management of varicose veins has not yet been determined

All laboratory methods demand ongoing quality control For deep vein thrombosis this means correlation of the instrumental results with venography clinical outcome and the findings at surgery and postmortem This is particularly true of Doppler ultrasound studies since the availability of the instrument may tempt untrained personnel to assign an unwarranted accuracy to their results

Arm and hand

Occlusive disease of the large arteries of the arm is easily detected by segmental systolic blood pressures with Doppler or plethysmographic pulse detection An exercise test can be performed

Clinical pharmacology of the new beta-adrenergic blocking drugs Part 12 Beta-adrenoceptor blockade in myocardial infarction the continuing controversy

William H Frishman M D*

Bronx N Y

Beta adrenoceptor blocking drugs have been shown to be safe and effective in the treatment of patients who have hypertension angina pectoris hypertrophic cardiomyopathy thyrotoxicosis, glaucoma and migraine headaches[1] However the role of these agents in the treatment and prevention of myocardial infarction is controversial due to a lack of adequately controlled clinical trials

These agents are employed with a view toward improving the quality as well as the quantity of life even though there is no adequate clinical data to prove the latter The theoretical considerations and clinical experience in the use of beta adrenoceptor blocking drugs during the acute phase of myocardial infarction and for the primary and secondary prevention of acute myocardial infarction and sudden death are assessed in this article

Primary prevention (myocardial infarction and sudden death)

While beta adrenoceptor blockade does not directly affect the progress of coronary atheroma it does reduce myocardial oxygen requirements This in turn enables the cardiac muscle to tolerate for a while what would otherwise be an inadequate supply of oxygen The reduction of oxygen requirements is due to a decreased heart rate and reduction in myocardial contractility Beta blockade may improve distribution of flow in the ischemic myocardium[4] as well as improve the utilization of myocardial substrate[5] These drugs are known to inhibit platelet aggregation and to be potent antiarrhythmic agents[5]

In patients with angina pectoris these agents have been useful in reducing pain and improving exercise tolerance An adequate degree of beta adrenoceptor blockade affords marked relief from pain in 80% of cases This success rate can be improved by selecting the best tolerated beta blocker in combination with nitrates Thus the quality of life can be improved in patients with angina pectoris

A major unresolved question in clinical medicine is whether the beta adrenoceptor blockers can influence the natural course of stable angina pectoris by prolonging the patient s life expectancy and by reducing the risk of infarction There are multiple subgroups of patients with angina pectoris defined by differences in symptomatology (stable or unstable) coronary anatomy left ventricular function and stress test results These multiple variables make a proper study design almost untenable The few poorly designed studies that have been completed have not demonstrated any marked reduction in the annual mortality rate of patients with stable angina pectoris when compared to results of large epidemiologic studies While patients are treated with beta adrenoceptor blockers to increase the

From the D[illegible] Albert Einstein College of M[illegible]

Received for publication [illegible]

Reprint requests William H F[illegible] M D [illegible] Cardiology Albert Einstein College [illegible] M[illegible] Bronx N Y 10461

*Dr Frishman is a Teaching [illegible] American Heart Association

0002-8703/80/040528 + 00$00.80/0 © 1980 The C V Mosby Co

quality and quantity of life only the quality of life has proven to be enhanced

Nevertheless beta blockade is the treatment of choice for the symptomatic relief of angina pectoris However as in the case with lipid lowering and platelet inhibiting agents only theoretical considerations suggest employing beta adrenoceptor blocking drugs as primary prophylactic treatment against myocardial infarction and sudden death Prospective studies with high risk individuals are necessary to determine whether primary preventive treatment will indeed prolong life and/or prevent sudden death In lieu of definitive proof of efficacy primary prophylactic treatment is cost ineffective

While no definitive evidence exists for the primary prophylactic benefits of beta adrenoceptor blocking drugs preliminary data suggest that these drugs may be useful in the secondary prevention of reinfarction and sudden death [1]

Beta adrenoceptor blocker therapy in acute myocardial infarction

In patients with acute myocardial infarction the presence of severe pain tissue injury and circulatory disturbances are important physiological stresses which trigger an increased sympatho adrenal discharge This observation is based on evidence derived from several studies of urinary free catecholamine excretion [1] and measurements of plasma catecholamine levels during the early stages of myocardial infarction [1]

An increase in circulating catecholamine levels following myocardial infarction may have an important supportive role in the maintenance of the contractile performance of ischemic areas of the myocardium as well as enhancing the residual non ischemic areas However there are two important and potentially deleterious consequences of an increase in sympathetic nervous activity

1 Increased sympatho adrenal discharge may be the cause of serious cardiac arrhythmias after myocardial infarction

2 The positive inotropic and chronotropic effects of catecholamines lead to an increase in total cardiac work and myocardial oxygen consumption This may be critical particularly in areas of ischemia at the border of an infarct in which increased oxygen demands may extend areas of necrosis Isoproterenol has been shown to impair both performance and metabolism of an ischemic myocardium which suggests that enhanced neuro adrenergic activity may be harmful

Beta adrenoceptor blocking drugs have logically been considered for use in patients with acute myocardial infarction to prevent the undesirable consequences of increased sympatho adrenal discharge These agents favorably influence some of the determinants of myocardial oxygen consumption On the other hand beta adrenoceptor blockade can have dangerous consequences in some cases of fresh infarction Impulse formation may be greatly impaired and conduction diminished to a degree that causes cardiac arrest Furthermore exacerbation of congestive heart failure due to the elimination of the positive inotropic effect of catecholamines has been a known sequela of beta blockade

Antiarrhythmic effects The value of beta adrenoceptor blockade in patients with dysrhythmias has been established However the antiarrhythmic efficacy of beta blockade in acute myocardial infarction has not been well documented

The arrhythmogenic actions of catecholamines have been recognized for over 70 years Recently it has been found that removal of sympathetic influences to the heart by whatever means will lead to a reduction in the incidence of arrhythmias following experimental coronary occlusion in animals Furthermore the occurrence of ventricular arrhythmias in experimental infarction was found to be associated with increased levels of catecholamines [7]

The exposure of ischemic tissue to high levels of catecholamines favors the appearance of multiple re entry pathways and the development of ventricular tachyarrhythmias and ventricular fibrillation [ ] These experimental data suggest that beta blockade would be particularly effective in preventing or aborting arrhythmias in acute myocardial infarction

Experimental studies in dogs with myocardial infarction revealed that pretreatment with beta adrenoceptor blockers prevented or reduced the incidence of malignant ventricular tachyarrhythmias

Randomized controlled trials comparing propranolol and alprenolol to placebo in patients with acute myocardial infarction have not revealed differences in the incidence of mortality or morbidity (heart failure or arrhythmia)

These studies have been criticized for failing to measure plasma durg levels and for using a fixed dose regimen rather than titrating the drug to the patient's requirements.

Lemberg and colleagues[41] reported the first major experience using beta blockers in the elective management of arrhythmias after acute myocardial infarction. These investigators reported favorably on the elective use of propranolol in 34 patients who had 43 episodes of tachyarrhythmia following an acute myocardial infarction complicated by mild to moderate heart failure. The dosage of propranolol employed in these studies was 0.5 to 0.75 mg intravenously given at 2 minute intervals until sinus rhythm returned or the ventricular rate slowed down to 80 beats/minute. The arrhythmias included examples of atrial fibrillation, atrial flutter, supraventricular tachycardia and ventricular tachycardia, all with ventricular rates over 140 beats/minute. A majority of patients responded to a total intravenous dose of less than 5 mg of propranolol.

Lemberg and co-workers also investigated the use of alprenolol in acute cardiac arrhythmias in patients with infarction and found the drug to be as effective as propranolol in both supraventricular and ventricular arrhythmias. The average intravenous dose was 9.5 mg (range 2 to 20 mg). Comparable experiences with oxprenolol and practolol have been reported.

Beta adrenoceptor blockers have been proved efficacious in the treatment of many patients with atrial fibrillation, atrial flutter, paroxysmal supraventricular tachycardia, junctional tachycardia, and lidocaine resistant ventricular arrhythmias. These drugs may be used adjunctively with other antiarrhythmic agents as well as in dc electrocardioversion. Over all, the beta adrenoceptor blocking drugs are more effective in paroxysmal supraventricular tachyarrhythmias than they are for ventricular rhythm disturbances.

The therapeutic efficacy of beta adrenoceptor blockade as an antiarrhythmic intervention is well accepted. However, potential side effects must be considered when employing beta blocking drugs. These agents can cause or potentiate congestive heart failure, hypotension, atrioventricular conduction delay and airway obstruction. It is for these reasons that the routine prophylactic administration of these drugs to all patients with acute myocardial infarction is not justified without hemodynamic monitoring. When using beta blockers as antiarrhythmic agents in acute myocardial infarction, the dele-terious effects of tachyarrhythmias in hemody-namic terms and the benefits of reversion to ... rhythm or slowing of the rapid ventricular ra... must be balanced against the possible cardiova-scular depression produced by the drugs them-selves.

Whether or not beta adrenoceptor block... drugs with intrinsic sympathomimetic acti... (pindolol, acebutolol, oxprenolol) will provide saf-er antiarrhythmic alternatives to propranolol h... not been proven in clinical trials.

Reduction or containment of myocardial infarction. Beta adrenoceptor blockers would b... used extensively in acute myocardial infarcti... were it not for their negative inotropic effe... beta adrenergic activity is important for disease... hearts.

The negative inotropism of these drugs rela... to anti-adrenergic effects rather than membra... depressing properties. The negative inotro... effect of beta adrenergic blockade is not clinica... important without evidence of left ventricul... dysfunction.

Early clinical studies (prior to 1970) in acute myocardial infarction, where oral proprano... was employed as a prophylactic agent, revealed no clinical benefit. After these prelimin... results, beta adrenoceptor blockers were not used in myocardial infarction until the 1970s. Th... use was suggested when investigators recom... that the development of irreversible left ventric-lar pump failure was related to the area of damaged myocardium, emphasizing a need t... preserve the ischemic myocardium. It is now well established that myocardial infarction is not an all or none phenomenon. It has been shown th... there is an ischemic region around the ... infarcted area that may not necrose until sever... hours or days have elapsed.[55] It has been dem-onstrated that reduction of myocardial oxyg... requirements will decrease the final size of a... infarct and an increase in oxygen requiremen... will increase the infarct. In dogs with ... experimental occlusion of a coronary artery, pro-pranolol will reverse the epicardial ST segme... elevation of the electrocardiogram ... which are said to reflect a reduction in th... predicted size of the myocardial infarction. Of interest is the fact that exogenous catecholam... have been found to have the reverse effect.

In man, Pelides and colleagues have s... that practolol given within 72 hours of an ...

reduced the precordial ST segment elevation. These findings were amplified by Mueller and co-workers who demonstrated a reduction of myocardial hypoxia as estimated by increased lactate uptake in patients (Class I and II New York Heart Association Classification) after intravenous propranolol was administered within the first 12 hours of infarction. In the study by Mueller and associates, there was no deterioration in clinical left ventricular function. Reductions in cardiac contractility, cardiac index, and myocardial oxygen consumption in patients were associated with improved myocardial metabolism and bioenergetics. Despite these favorable hemodynamic and metabolic findings, the investigators could not demonstrate an absolute decrease in infarct size or an increase in ultimate survival. *The difficulties in assessing a reduction in predicted myocardial infarction size are due to problems with the measuring modalities.*

Gold and co-workers recently demonstrated a reduction in ischemic injury (defined by reduction of ST segment elevation) on the ECG when intravenous propranolol was given during acute myocardial infarction. These effects were less marked, however, in patients with total coronary occlusions. These findings suggest that (1) propranolol may be more effective in subendocardial wall infarction where flow is not completely compromised and in this case ischemia may be a more important component than necrosis; (2) propranolol may be less effective in transmural myocardial infarction with more complete cessation of effective flow and where necrosis may greatly overshadow reversible ischemia. Nevertheless, these data suggest that a reduction in myocardial oxygen demand might arrest the stepwise progression of myocardial necrosis.

The results of a study by Cairns and co-workers demonstrated that propranolol administered an average of 7.6 hours after acute myocardial infarction in 20 patients appeared to delay the evolution of infarction. In a randomized double blind clinical trial by Pitt and colleagues, propranolol was shown to reduce infarct extension.

The benefit-to-risk ratio must be calculated for each patient prior to the use of beta adrenoceptor blockade in acute myocardial infarction. There are inherent problems with this therapy that must be considered.

1. Beta adrenoceptor blockers may increase left ventricular volume and end diastolic pressure by their negative inotropic effects, especially in severely damaged hearts. By this mechanism they may increase the oxygen demands of ischemic myocardial tissue. At the same time, increased left ventricular end-diastolic pressure can limit an already compromised subendocardial blood flow. These risk factors could easily offset the beneficial reduction in heart rate and blood pressure with beta adrenoceptor blockade.

2. Since patients have varying degrees of sympathetic tone, there is no established beta adrenoceptor blocking dose with any agent. One patient might require a dose four times that of another patient to achieve the same beta blocking effect. The drug should also be given intravenously in acute myocardial infarction to achieve its immediate effects, and this might precipitate *sudden bradyarrhythmias or conduction abnormalities.*

3. Despite the adverse effects of isoproterenol recently defined in experimental animals with myocardial infarction, heightened sympathetic tone may not be deleterious for all patients. Some patients with a considerable amount of frank necrosis and little ongoing ischemia may need their sympathetic tone to preserve pump function. Beta adrenoceptor blockade could actually worsen cardiac failure in these patients.

The widespread administration of beta adrenoceptor blocking agents to patients with myocardial infarction is not indicated unless hemodynamic monitoring is available to assess the benefit-to-risk ratio in any given patient. Where ischemia rather than necrosis is the cause of the pathological problem, beta adrenoceptor blockade is recommended, especially in those patients with preinfarction states ("intermediate syndrome"). By decreasing heart rate, blood pressure, and contractility, beta adrenoceptor blockade reduces ischemia and relieves pain. Left ventricular function, which may be transiently depressed in acute ischemia, generally improves as the ischemia is lessened. Once the situation is stabilized medically, more definitive measures, including coronary angiography and, when appropriate, coronary artery bypass surgery, may be considered.

Excluding patient contraindications, the recommended dose of propranolol for treatment of acute and prolonged myocardial ischemia is 0.05 to 0.10 mg/kg (lean body weight) administered intravenously at a rate of 1 mg/minute. [This] should be followed by an oral dose

designed to achieve adequate beta adrenoceptor blockade

The potentially protective properties of propranolol in acute myocardial ischemia in the absence of infarction have been reported by several groups In a randomized double blind study of 68 patients with unstable angina the propranolol treated patients experienced fewer coronary events than placebo treated patients In patients admitted to a coronary care unit because of prolonged ischemic chest pain a myocardial infarction developed less frequently under long term treatment with beta adrenoceptor blocking drugs 30 to 90 patients experienced infarction in contrast to 62 of 90 patients who did not receive the drug

Beta adrenoceptor blocking drugs are indicated when angina pectoris develops after acute myocardial infarction and in a subgroup of patients with myocardial infarction associated with a hyperkinetic circulatory response (i e hypertension tachycardia) without evidence of left ventricular dysfunction

The results of experimental and clinical research suggest that beta adrenoceptor blockade can play an important role in the treatment of acute myocardial infarction This blockade decreases cardiac work and improves perfusion and metabolism of ischemic myocardium The effectiveness of beta adrenoceptor blocking agents primarily depends upon the functional state of the heart The more left ventricular function is determined by the mechanical and contractile properties of ischemic areas the more likely beta adrenoceptor blockade will improve oxygenation of the jeopardized myocardium However a deleterious effect can be anticipated when the ventricular performance is primarily determined by frank myocardial necrosis With careful evaluation of the benefits to risk potential in individual patients beta adrenoceptor blockade can be a useful therapeutic intervention for protecting the ischemic myocardium in acute myocardial infarction

Secondary prevention of myocardial infarction and sudden death

There is currently a 10% mortality rate one year following a myocardial infarction and this mortality occurs within one hour of the onset of symptoms in approximately half of these cases[11] A therapeutic goal is to decrease the mortality rate in this group of patients who ar[e at] high risk of sudden death Ventricular tach[y]rhythmias are now considered the most im[por]tant cause of sudden death in patients who [are] less than 70 years old

A significant reduction in mortality by con[tin]uous treatment with procainamide quinid[ine] phenytoin as well as other new antiarrhyth[mic] agents after myocardial infarction has not b[een] demonstrated in controlled clinical trials Short term trials using propranolol follow[ing] acute myocardial infarction have shown conf[lict]ing results Snow in 1965[7] first reported a s[ub]stantial reduction of mortality in patients w[ith] myocardial infarction who had received propr[an]olol He treated 52 patients with 60 mg [of] propranolol daily for 21 days and compared th[em] to 55 control subjects The results while imp[res]sive were not conclusive because it was an op[en] label study without a double blind control gro[up] Several randomized double blind studies w[ere] then initiated These included about 250 patie[nts] with acute myocardial infarction who received [an] average of 40 to 80 mg of oral propranolol da[ily] These controlled studies failed to confirm t[he] findings of Snow There were no significa[nt] differences in mortality shock heart fail[ure] hypotension or arrhythmias between the trea[ted] and the untreated patients

The first long term study using a beta adren[o]ceptor blocker also failed to demonstrate decreased mortality rate In this double bl[ind] randomized study by Reynolds and Whitl[ock] (Table I) 78 patients were given 100 mg alprenolol or placebo four times daily for o[ne] year following the time of admission to a ho[s]p[ital] coronary care unit This trial may have been too short a duration and may have involved t[oo] few patients to show a difference

Two major clinical trials from Sweden u[sing] alprenolol in patients with myocardial infarct[ion] have since been completed Alprenolol w[as] chosen as the beta adrenoceptor blocker for stu[dy] owing to its moderate intrinsic stimulat[ory] action and consequent theoretically red[uced] risk of causing sinus bradycardia The objectiv[es] of these studies were to investigate whether t[he] incidence of recurrence of infarction s[udden] death and total mortality was influenced [in] patients treated with a beta adrenoceptor How[ev]er

In the study by Wilhelmsson and colleag[ues]

Table I Reported efficacy of long term beta adrenoceptor blockade in preventing reinfarction and sudden death

Study	*Patients (no)*	*Duration of Study*	*Regimen*	*Non fatal reinfarction*	*Sudden death*	*Total mortality*
Reynold and Whitlock	78	1 year	Alprenolol (39) Placebo (39)	4 4 (NS)	2 1 (NS)	3 3 (NS)
Wilhelmsson et al	230	2 years	Alprenolol (114) Placebo (116)	16 18 (NS)	3 11 ($p < 0.05$)	7 14 (NS)
Ahlmark et al	162	2 years	Alprenolol (69) No therapy (93)	4 15 ($p < 0.05$)	1 9 ($p < 0.05$)	5 11 (NS)
International Multicentre Study	3 038	Up to 3 years (mean in 14 months)	Practolol (1 514) Placebo (1 524)	69 89 ($p < 0.10$)	30 52 ($p < 0.02$)	47 73 ($p < 0.02$)

NS = not statistically significant
Study had to be terminated because of major toxic effects of practolol
Reduction in total cardiac mortality rate was only significant for patients with previous anterior wall myocardial infarction

(Table I) patients who had a myocardial infarction were less prone to sudden death if treated with a beta blocking drug In this small but well controlled study 230 patients who had sustained a myocardial infarction were grouped into four separate risk strata which were determined by the degree of previous myocardial damage Within each stratum alprenolol (400 mg daily) or placebo was randomly assigned to patients over two years Within each stratum the incidence of non fatal reinfarction appeared much the same but the incidence of sudden death and total mortality was significantly reduced in patients receiving alprenolol These results have been questioned because of the use of a fixed dose regimen and the small sample size analyzed

In the study by Ahlmark and co workers a similar reduction in sudden death was seen in patients treated with alprenolol compared to matched controls In contrast to the findings of Wilhelmsson and colleagues these investigators also reported a reduction in the actual reinfarction rate in patients receiving alprenolol This single blind randomized trial was carried out for two years in 162 patients who had sustained a myocardial infarction (Table I) Patients received either 100 mg of alprenolol four times daily or no beta blocker This study has been criticized on the grounds that the patients were randomized before their eligibility for the study was determined and because the study was open and the control group was not given placebo

Alprenolol was well tolerated in the three trials as demonstrated by the low patient drop out rate because of drug intolerance It was concluded that alprenolol could be safely administered to patients with acute myocardial infarction excluding those patients with conduction disease active bronchospasm and congestive heart failure

The largest trial of a beta adrenoceptor blocker to date in patients with myocardial infarction was a double blind randomized multicenter international study in over 3 000 patients comparing practolol with placebo (Table I) One to four weeks after an acute myocardial infarction fixed dose practolol (200 mg twice daily) or placebo was randomly assigned to patients Unfortunately the trial was prematurely terminated after the reports of practolol toxicity emerged However 330 actively treated patients and 336 treated with placebo were followed for over two years A significant difference was found in the incidence of sudden death within two hours after the onset of symptoms—30 patients in the practolol group compared with 52 patients in the placebo group There was also a significant difference in the total number of cardiac deaths A non significant trend toward reduction in non fatal reinfarctions 69 compared with 89 was also found In this study the beneficial effects seem to be confined to patients with previous anterior wall myocardial infarcts and low diastolic blood pressures at entry The study also showed a significant reduction in cardiac arrhythmias and in the incidence of angina pectoris with practolol

The evidence in favor of a prophylactic or cardioprotective effect of beta adrenoceptor blocking drugs in the management of patients following myocardial infarction is persuasive At least three possible mechanisms of action might be implicated Chronic beta adrenoceptor block

ade might prevent myocardial infarction by (1) reducing myocardial oxygen demands[5] and/or altering abnormal platelet aggregability[6] (2) by preventing malignant arrhythmias during the initial phase of an infarction and (3) by influencing the size of the ischemic area apart from the antiarrhythmic action of the beta blocker irrespective of whether infarction occurred[30]

Would one beta adrenoceptor blocking agent provide a theoretical advantage over another in patients with acute myocardial infarction? With equal degrees of beta adrenoceptor blockade all the available agents are equally effective in the therapy of hypertension arrhythmias and angina pectoris[1,4] Alprenolol a non cardioselective agent with membrane stabilizing activity and intrinsic agonist effects and practolol an agent which has cardioselective and agonist activities without membrane depressant effects both appear useful as cardioprotective agents Therefore it would appear that if beta adrenoceptor blockade proved to be an effective treatment modality in patients with myocardial infarction all the beta blocking drugs could be interchanged with the exception of small differences in side effects

The observations made with alprenolol and practolol need to be confirmed and extended to larger patient populations There were major methodological problems with both the alprenolol and practolol trials Currently the National Institute of Health is sponsoring a large multicenter trial (Beta Adrenoceptor Blocker Heart Attack Trial BHAT) evaluating long term oral propranolol therapy in patients with myocardial infarction This study was designed to eliminate some of the methodological problems of previous trials Patients who meet entry criteria will be randomly assigned to receive placebo and propranolol treatment five days after infarction Propranolol is titrated from 180 to 240 mg daily to achieve effective beta adrenoceptor blockade Serum levels are being monitored and patients are observed for up to four years A patient cohort of over 4 000 is being evaluated The data to be collected include the incidence of sudden death non fatal reinfarction fatal myocardial infarctions (not sudden death) non cardiovascular deaths arrhythmia and angina pectoris A similar multicenter trial comparing metoprolol (a cardioselective agent) with placebo is now being planned

These well-controlled studies will undoubtedly yield conclusive results that will la[y the] controversy to rest It is anticipat[ed that beta] adrenergic blockade will be proved [not only] safe and effective in the managemen[t of ischemic] heart disease but also in the preve[ntion of in]farction

Conclusions

The results of experimental [and clinical] research suggest that beta adrenoce[ptor blockers] may play an important role in the pr[evention and] treatment of acute myocardial inf[arction. They] decrease cardiac work and impro[ve myocardial] metabolism The drugs are also eff[ective anti]rhythmic agents

Beta adrenoceptor blockers sign[ificantly re]duce the symptoms of angina pecto[ris but have] not been shown to influence the [mortality in] patients in primary prevention tria[ls. After] acute myocardial infarction howe[ver there is] some evidence suggesting that chron[ic beta adre]noceptor blocker therapy can red[uce the inci]dence of sudden death and reinfarct[ion]

In the treatment of acute myoc[ardial infarc]tion the effectiveness of beta adreno[ceptor block]ade depends upon the functional [state of the] heart The more left ventricular func[tion is deter]mined by the mechanical and contra[ctile proper]ties of ischemic areas the more lik[ely it is that] beta adrenoceptor blockade will imp[rove the oxygen]ation of jeopardized myocardium [...] hemodynamic monitoring of patient[s ...] benefits and potential hazards can [...] The early use of beta adrenoceptor b[lockers may] interrupt the stepwise development o[f myocardial] necrosis may salvage myocardial tis[sue and] improve immediate mortality rate a[nd left] ventricular function

Future studies will determine w[hether beta] adrenergic blocking drugs can enhan[ce the quan]tity of life as well as the quality of lif[e of patients] who have sustained a myocardial in[farction]

REFERENCES

1 Frishman W., and Silverman R Clinica[l pharmacology] of the new beta adrenergic blocking drug[s ... com]parative clinical experience and new ther[apeutic applica]tion. Am Heart J 98 119 1979
2 Conolly M E Kersting F and Dolle[ry CT The] clinical pharmacology of the beta adreno[ceptor blocking] drugs Progr Cardiovasc Dis 19 203 19[76]
3 Epstein S E Robinson B F Kahl[er RL] Braunwald E Effect of beta adrenerg[ic blockade on] the cardiac response to maximal and sub[maximal exer]cise in man J Clin Invest 44 1 [...] 1[965]
4 Becker L C., Fortuin N J and Pitt [...]

ischemic and anti anginal drugs on the distribution of radioactive microspheres in the canine left ventricle Circ Res 28 263 19 1
5 Opie L H and Thomas M Propranolol and experimental myocardial infarction substrate effects Postgrad Med J 52(Suppl 4) 124 1976
6 Frishman W H Weksler B Christodoulou P Smithen C and Killip T Reversal of abnormal platelet aggregability and change in exercise tolerance in patients with angina pectoris following oral propranolol Circulation 50 887 1974
7 Jewitt D E and Singh B N The role of β adrenergic blockade in myocardial infarction Progr Cardiovasc Dis 16 421 1974
8 Prichard B N C and Gillam P M S Assessment of propranolol in angina pectoris Br Heart J 33 473 1971
9 Wiener L Dwyer E M Jr and Cox J W Hemodynamic effects of nitroglycerin propranolol and their combination in coronary heart disease Circulation 39 623 1969
10 Amsterdam E A Wolfson S and Gorlin R Effect of therapy on survival in angina pectoris Ann Intern Med 68 1151 1968
11 Lambert D M D Long term survival on beta receptor blocking drugs in general practice—a three year prospective study *in* Hypertension—its natural history and treatment Int Symp Malta Burley D et al editors, London England 19 5 Ciba p 283
12 Russek H I Prognosis in angina pectoris with optimal medical therapy *in* New Horizons in Cardiovascular Practice Russek H I ed Baltimore 1975 University Park Press
13 Warren S G Brewer D L and Orgain E S Long term propranolol therapy for angina pectoris Am J Cardiol 37 420 1976
14 Kannel W B and Feinlab M Natural history of angina pectoris in the Framingham study Prognosis and Survival, Am J Cardiol 29 154 1972
15 Wilhelmsson C Vedin J A Wilhelmsen L Tibblin G and Werko L Reduction of sudden deaths after myocardial infarction Lancet 2 1157 1974
16 Ahlmark G Saetre H and Korsgren M Reduction of sudden deaths after myocardial infarction Lancet 2 1563 19 4
17 Multicentre International Study Improvement in prognosis of myocardial infarction by long term beta adrenoceptor blockade using practolol Br Med J 1 837 19 6
18 Valori C Thomas M and Shillingford J P Free noradrenaline and adrenaline excretion in relation to clinical syndromes following myocardial infarction Am J Cardiol 20 605 1967
19 Jewitt D E Mercer C J Reid D Valor M Thomas M and Shillingford J P Free noradrenaline and adrenaline excretion in relation to the development of cardiac arrhythmias and heart failure in patients with acute myocardial infarction Lancet 1 635 1969
20 Gazes P C Richardson J A and Woods E F Plasma catecholamine concentrations in myocardial infarction and angina pectoris Circulation 19 657 1959
21 McDonald L Baker C Bray C McDonald A and Restieaux N Plasma catecholamines after cardiac infarction Lancet 2 1021 1969
22 Frishman W H and Sonnenblick E H Propranolol therapy in acute myocardial infarction Cardiovasc Med 2 311 1977
23 Vasu M A O Keefe D D Kapellakis G Z Daggett W M and Powell W J Jr Myocardial oxygen consumption and hemodynamic effects of dobutamine epinephrine and isoproterenol Fed Proc 34 435 1975
24 Maroko P R Kjekshus J K Sobel B E Watanabe T Covell J W Ross J Jr and Braunwald E Factors influencing infarct size following experimental coronary artery occlusions Circulation 43 67 1971
25 Gunnar R M Loeb H S Pietras R J and Tobin J R Jr Ineffectiveness of isoproterenol in shock due to acute myocardial infarction JAMA 202 1124 1967
26 Mueller H Ayres S M Fianelli S Jr Conklin E F Mazzara J T and Grace W J Effect of isoproterenol l norepinephrine and intra aortic counterpulsation on hemodynamics and myocardial metabolism in shock following acute myocardial infarction Circulation 43 335 1972
27 Kirk E S Hirzel H O and Sonnenblick E H The relative role of supply and demand in the effect of isoproterenol on infarct size Circulation 55 and 56(Suppl 3) III 149 1979
28 Black J W Drug Responses in Man London 1967 Little Brown & Company p 191
29 Epstein S Goldstein R Redwood D R Kent K M and Smith E R The early phase of acute myocardial infarction pharmacologic aspects of therapy Ann Intern Med 78 918 1973
30 Brunner H The pharmacological basis for the cardioprotective action of beta blockers *in* The Cardioprotective Action of Beta Blockers Gross F ed Baltimore 19 6 University Park Press p 11
31 Schaal S F Wallace A G and Sealy W C Protective influence of cardiac denervation against arrhythmias of myocardial infarction Cardiovasc Res 3 241 1969
32 Ebert P A, Vanderbeck R B Allgood R J and Sabiston D C Effect of chronic cardiac denervation on arrhythmias after coronary artery ligation Cardiovasc Res 4 141 19 0
33 Ceremuzynski L Staszewska Barczak J and Herbaczynska Cedro K Cardiac rhythm disturbances and the release of catecholamines after coronary occlusion in dogs Cardiovasc Res 3 190 1969
34 Han J Mechanisms of ventricular arrhythmias associated with myocardial infarction Am J Cardiol 24 800 1969
35 Khan M I Hamilton J T and Manning G W Protective effects of beta adrenoceptor blockade in experimental coronary occlusion in conscious dogs Am J Cardiol 30 832 1972
36 Balcon R Jewitt D E Davies J P H and Oram S A controlled trial of propranolol in acute myocardial infarction Lancet 2 917 1966
37 Clausen J Felsby M Jorgensen F Nielsen B L, Roin J and Strange B Absence of prophylactic effect of propranolol in myocardial infarction Lancet 2 920 1966
38 Norris R M Caughey D E and Scott P J A trial of propranolol in acute myocardial infarction Br Med J 2 398 1968
39 Stephen S A Unwanted effects of propranolol Am J Cardiol 18 463 1966
40 Briant R and Norris R M Alprenolol in acute myocardial infarction N Z Med J 71 135 19 0
41 Lemberg L Castellanos A and Arcebal A G The use of propranolol in arrhythmias complicating acute myocardial infarction Am HEART J 80 4 9 19 0
42 Lemberg L Arcebal A G Castellanos A and Slavin D Use of alprenolol in acute cardiac arrhythmias Am J Cardiol 30 77 1972
43 Sandler G and Pistevos A C Use of oxprenolol in cardiac arrhythmias associated with acute myocardial infarction Br Med J 1 254 1971
44 Jewitt D E and Croxson R Practolol in the manage

ment of cardiac dysrhythmias following myocardial infarction and cardiac surgery Postgrad Med J 47 (Suppl) 25 1971
45 Frishman W Clinical pharmacology of the new beta adrenergic blocking drugs Part 1 Pharmacodynamic and pharmacokinetic properties AM HEART J 97 663 1979
46 Frishman W and Silverman R Clinical pharmacology of the new beta adrenergic blocking drugs Part II Physiologic and metabolic effects AM HEART J 97 797 1979
4 Vogel J H K and Blount S G Jr Modification of cardiovascular responses by propranolol Br Heart J 29 310 1967
48 Epstein S E and Braunwald E Clinical and hemodynamic appraisal and beta adrenergic blocking drugs Ann N Y Acad Sci 139 952 1967
49 Wolk M J Scheidt S and Killip T Heart failure complicating acute myocardial infarction Circulation 45 1125 1972
50 Mueller H S Ayres S M Religa A and Evans R G Propranolol in the treatment of acute myocardial infarction effect on myocardial oxygenation and hemodynamics Circulation 49 1078 1974
51 Alderman E L Coltart D J Robinson S C and Harrison D C Effects of propranolol on left ventricular function and diastolic compliance in man Circulation 48(Suppl 4) 87 1973
52 Manning J P Pen inger R R and Fehn P A Cardiac alkaline phosphatase activity potassium concentration in dogs with acute myocardial infarction Cardiovasc Res 2 308 1968
53 Cox J L McLaughlin V W Flowers N C and Horan L C The ischemic zone surrounding acute myocardial infarction Its morphology as detected by dehydrogenase staining AM HEART J 76 650 1968
54 Raab W The nonvascular metabolic myocardial vulnerability factor in coronary heart disease AM HEART J 66 685 1963
55 Maroko P R and Braunwald E Modification of myocardial infarction size after coronary occlusion Ann Intern Med 79 720 1973
56 Redwood D R Smith F R and Epstein S E Coronary artery occlusion in the conscious dog Effects of alteration in heart rate and arterial pressure on the degree of myocardial ischemia Circulation 46 323 1972
57 Shell W E and Sobel B E Deleterious effects of increased heart rate on infarct size in the conscious dog Am J Cardiol 31 474 1973
58 Herbaczynska Cedro K The influence of adrenaline secretion on the enzymes in heart muscle after acute coronary occlusion in dogs Cardiovasc Res 4 168 1970
59 Pelides L J Reid D S Thomas M and Shillingford J P Inhibition by beta blockade of the ST se elevation after acute myocardial infarction in Cardiovasc Res 6 295 19 2
60 Gold H K Leinbach R C and Maroko Propranolol induced reduction of sign of ischemic during acute myocardial infarction Am J C 38 689 1976
61 Cairns J S and Klassen G Modification of myocardial infarction by IV propranolol Circ 52(Suppl 2) 107 1975
62 Pitt B Weiss J L Schulze R A Tayl r Kennedy H L and Caralis D Reduction of m dial infarct extension in may by propranolol Circ 54(Suppl 2) 29 1976
63 Frishman W Smithen C Befler B Kli field, Killip T Non invasive assessment of clinical re to oral propranolol Am J Cardiol 35 635 19 5
64 Chidsey C and Vogel J Adrenergic mechan heart failure *in* Cardiovascular Beta Adr Responses Kattus A A Ross G and Hall, V E Berkely 1970 University of California Press, p 8
65 Haneda T Lee T., and Ganz W Metabolic eff propranolol in the ischemic myocardium tud residual sampling Circulation (Suppl 4) 1 4 197
66 Davies R O Mizgala H F Tinmouth A L W D D and Counsell J Pro pective controlled t long term propranolol on acute coronary eve patients with unstable coronary artery disease stract) Clin Pharacol Ther 17 232 1975
67 Fox K M Chopra M P Portal R W and Aber Long term beta blockade possible protection from cardial infarction Br Med J 1 117 19 5
68 Guazzi M Beta blockade in hyperkinetic hear drome *in* The Cardioprotective Action of Beta Bl Baltimore 1976 University Park Press, p 46
69 Pell S and d Alonzo C A Immediate mortali five year survival of employed men with a first m dial infarction N Engl J Med 270 915 1964
70 Norris R M and Mercier C I Long term pr following treatment in a coronary care unit Aust Med 1 31 1973
71 Romo M Factors related to udden d aths in ischemic heart disease Acta Med Scand (Suppl 1973
72 Kosowsky B D Taylor J Lown A and Ritchie Long term use of procainamide following acute m dial infarction Circulation 47 1204 19 3
73 Collaborative Group Phenytoin after recovery myocardial infarction Lancet 2 1055 1
74 Snow P J D Effect of propranolol in myoc infarction Lancet 2 551 196
75 Reynold J L and Whitlock R M L Effect beta adrenergic receptor blocker in myocardial i tion treated for one year from onset Br Heart J 3 1972

Microscopy of urine—now you see it now you don't!

Nearly all presently performed routine microscopic examinations of the urine are practically useless and some results are dangerous.

The detection of abnormal numbers of casts white or red blood cells in urine is probably the most sensitive index of the presence of urinary tract pathology although for casts up to the present time this has not been studied in a thorough and systematic fashion with modern techniques. A simple calculation on the relation between the kidneys tendency to hypertrophy after nephrectomy and presumably also after slowly progressive nephron destruction such as that due to glomerulonephritis, implies that even an accurately measured glomerular filtration rate will not show a change until about 40% of the nephron population has been destroyed. Therefore the earliest changes will only be detectable by histological examination of the kidney or by accurate and careful examination of the urine.

However presently employed techniques of urinary microscopy by routine hospital and private pathological laboratories whether by centrifugation of the urine and examination of the sediment on an ordinary microscope slide and reporting a per high power field (HPF) or by examination of an uncentrifuged specimen is in our experience useless and an enormous waste of public money. We have shown that with a semiquantitative technique employing centrifugation of the early morning specimen and examination of the sediment in a counting chamber good correlation can be obtained with renal functional abnormalities and abnormal numbers of casts red cells and white cells in a single examination. When the same urine specimens were examined by the routine laboratory in a renally oriented hospital employing the HPF technique the correlation with renal functional abnormalities was much less. Particularly significant was the fact that in two out of four patients with histologically proven glomerulonephritis the HPF technique did not detect casts whereas the semiquantitative technique did so in all cases. Evaluation of the two techniques was retrospective and although not specifically blind the diagnoses were unknown at the time of renal functional testing and urine examination.

Increasingly frequent claims are being made of the presence of silent glomerulonephritis—i.e. histologically documented glomerulonephritis yet completely normal urine sediment. In our experience this is not so although a stressed before a systematic prospective study of this has not yet been performed. All previous studies have employed these unsatisfactory HPF methods. In this regard a recent report on severe Goodpasture's syndrome without significant renal pathology is of particular interest since the authors were unable to find abnormalities in the urinary sediment when examined by a technique similar to the ones proposed. Histology only showed mild linear immunofluorescent deposition but no light microscopic change. Whether the immunofluorescent deposition signified renal pathology of course is questionable.

A more recent practice is to examine an uncentrifuged specimen for white cells and red cells and express them as numbers per microliter of urine. Although this method has been shown to reflect reliably the number of cells per microliter particularly at high cell excretion rates it is entirely unsuitable for looking for casts—most physicians probably do not realize this and interpret a report showing no casts *seen* as reliably indicating no casts *present* in the urine. Although we have not quantitated our available data to compare the uncentrifuged data with our semiquantitative method as we did with the HPF method our impressions with another three hospital laboratories are that they are similarly unsatisfactory in detecting abnormal numbers of casts, white and red cells. This is of course not surprising. It is almost certain that presently employed routine techniques, unless performed by a nephrologist are useless and lead to gross underestimation of renal pathology on the one hand and to a number of unnecessary renal biopsies on the other probably because it is believed that one can have a normal urine sediment with significant renal pathology. In our opinion these methods of examining the urine should be abandoned for it is far better *not* to have a result of a microurine examination than to have a false one. This is of particular importance when one considers the necessity to do renal biopsies. If urine microscopy when thoroughly examined shows no abnormalities no biopsy should be performed unless for academic reasons and with the full consent of the patient having had this situation explained to him. This is all the more important because of a recent prospective report that followed renal biopsies. Seventeen out of 90 had significant perirenal hematomas detected by CAT scanning.

Although for casts normal excretion rates are difficult to define because of the possibility of fragmentation of them in our experience the levels we have quoted of about 15 per mL seem a reasonable compromise. Normal values for white cell excretion rates are better defined and a level between 2 000 and 3 000 (2 to 3 per ml or 1 per HPF) per milliliter of white cells and 500 and 1 000 (0.5 to 1 per mL less than 1 per HPF) red cells per milliliter are acceptable normal limits. There may be some variation if urines during the day are examined rather than early morning specimens as the latter will of course be more concentrated.

These normal limits for this technique have now been defined in 1 720 volunteers without a history of renal disease (Personal communication Prof. D Ferguson, School of Public Health Blood Pressure Study Sydney Australia). Preliminary analysis of these data showed that 95% had 3 000 WBC/mL or less 98% had 1000 RBC/mL or less and 99 6% had 15 casts/ml or less.

Addis was the first to introduce a scientific approach to quantify excretion rates of the formed elements of the urine. The upper limits of normal by this technique are however significantly lower at 8/ml for casts 800/ml for WBC and

0002 8 03/80/040537 + 0 $00 70/0 © 1980 The C V Mosby Co

200 mL for RBC presumably because of destruction of these elements when urine is collected and stored over 12 hour periods. The technique is cumbersome because of the necessity for a timed urine collection and the long time interval involved and it has been largely abandoned

We would therefore urge that present methods of performing urinary microscopy with overuse and inaccurate results should be abandoned The procedure should be performed by a nephrologist unless more stringent methodology is adopted by pathology laboratories. The excuse that these tests are being ordered too frequently is unsatisfactory it is better not to do them than to give a wrong result

Akos Z Gyory MD (Syd) FRACP
Associate Professor of Medicine
Alison M Kesson MB BS
Jane M Talbot MB BS
Department of Medicine
University of Sydney
at the Royal North Shore Hospital
St Leonards NSW 2065
Australia

REFERENCES

1 Kesson A M Talbot J M, and Gyory A Z. ... scopic examination of urine Lancet 2 809 197...
2 Mahajan S K, Ordonez N G Feitelson, P J e... Lupus nephropathy without clinical renal involve... Medicine 56 493 1977
3 Appel G B, Silva F G, Pirani, C L, et al. ... involvement in systemic lupus erythematos... Medicine 57 371 1978
4 Mathew T H, Hobbs J B, Kalowski S et ... Goodpasture s syndrome Normal renal diagnos... ings, Ann Intern Med 82 215 19...
5 Rosenbaum, R, Hoffsten P E, Stanley R J et al ... of computerised tomography to diagnose com... of percutaneous renal biopsy Kidney Int. 14 ... 19...
6 Addis T The number of formed elements in the ur... sediment of normal individuals J Clin. Invest. 2 ... 1926

Excess smoking in malignant hypertension*

James VI of Scotland and I of England was the first to condemn smoking publicly when he stated that it was a "custom loathsome to the eye hateful to the nose harmful to the brain and dangerous to the lungs." Few of his successors to the throne took heed of his words and indeed we are told that the last four Kings of Britain died of causes that may have been attributable to smoking. The list of such diseases is long and seems to be growing but until now hypertension has not been recognized. It has been shown that the act of smoking a cigarette causes a transient rise in blood pressure and that there is an increased mortality rate among smokers with hypertension but it has otherwise been demonstrated that smoking does not cause hypertension.

Two recent studies however one from Glasgow Scotland and the other from Birmingham England have shown that smoking is more common in a selected group of hypertensive subjects namely those with malignant phase hypertension By taking a diastolic pressure greater than 120 mm Hg with bilateral retinal hemorrhages and exudates as the criteria for inclusion in their study the Glasgow workers identified 8... patients with malignant phase hypertension and found that ...% were smokers By contrast only 4... to ...% of patients in three age-matched control groups smoked These differences were significant for the sexes separately and together for cigarette smoking alone and for all forms of smoking combined

As might be expected the malignant phase patients fared worse than their non malignant controls in respect of ... failure and mortality A more interesting observation wa... smoking had a strong association with renal fa... mortality within the malignant phase group The mea... creatinine of the smokers (2...4 μmol/L) was double that of non smokers (106 μmol/L) of the 18 patients with ... creatinine greater than 250 μmol/L, 1... were smokers a... an ex smoker When deaths were considered, the e... mortality was confined to smokers By contrast none of ... who had never smoked had died during follow up, ... reached a mean of 3 years

The Birmingham workers took as their criteria f... nant phase hypertension bilateral hemorrhages o... and studied 48 patients comprising whites, blacks, and ... They derived similar findings in that 6...% were ... in contrast to only 3...% of controls who smoked. The ... reached significance for all groups with the excep... women alone Both studies were performed retrosp... and in neither was it possible to say whether the n... cigarettes smoked was important

These results suggest that smoking may pred... malignant phase in a patient who is already hyperte... This may explain at least in part the higher mort... from hypertension in smokers. Clearly smoking is not ... cause of malignant hypertension as some of the patie... never smoked Most would agree that increased a... pressure is the primary factor and it has been argu... increased arterial pressure promotes intravascular co... tion so leading to the main features of the disease ... could act as a trigger at this stage of the process b... increasing platelet stickiness and viscosity of b...

*This work was supported by the MPC Blood Pressure Unit Western Infirmary Glasgow G11 6NT Scotland, to which all requests for reprints should be addressed

0025-... 03 80 040 38 + 0...5002... 01 19...0 The C... M...

known to increase the likelihood of arterial thrombosis he recently reported association of smoking with prolifera ve diabetic retinopathy may have a similar basi

Whatever the mechanism the message is clear Smoking is ommoner among patients with malignant phase hyperten ion Patients with malignant phase hypertension who smoke re more likely to have renal failure and hence or otherwise re more likely to die The case therefore for encouraging ypertensive patients already prone to cerebrovascular and schemic heart disease to give up smoking becomes even tronger James VI & I would certainly have agreed

Christopher Isles M R C P
Medical Registrar
Dumfries Royal Infirmary
Dumfries DG1 4AP
Scotland

REFERENCES

1 Cellina G U Honour A J and Littler W A Direct arterial pressure heart rate and electrocardiogram during cigarette smoking in unrestricted patients Am Heart J 89 18 1975
2 Doll R and Peto R Mortality in relation to smoking 20 years observations on male British doctors Br Med J 2 1525 1976
3 Ballantyne D Devine B L and Fife R Interrelation of age obesity cigarette smoking and blood pressure in hypertensive patients Br Med J 1 880 1978
4 Reid D D Holland W W and Rose G A An Anglo American cardiovascular comparison Lancet 2 1375 1967
5 Seltzer C C Effect of smoking on blood pressure Am Heart J 87 558 1974
6 Ball K and Turner R Smoking and the heart The basis for action Lancet 2 822 1974
7 Isles C, Brown J J Cumming A M Lever A F, McAreavey D Robertson J I Hawthorne V M Stewart G M Robertson J W, and Wapshaw J Excess smoking in malignant phase hypertension Br Med J 1 579 1979
8 Bloxham C A Beevers D G, and Walker J M Malignant hypertension and cigarette smoking Br Med J 1 581 1979
9 Pickering G W *in* High Blood Pressure London 1968 J & A Churchill, Ltd
10 Beilin L J Goldby F S and Mohring J High arterial pressure versus humoral factors in the pathogenesis of the vascular lesions of malignant hypertension Clin Sci Mol Med 52 111 1977
11 Gavras H Oliver N Aitchison J, et al Abnormalities of coagulation and the development of malignant phase hypertension Kidney Int 8(Suppl 5) S-52 1975
12 Levine P H An acute effect of cigarette smoking on platelet function A possible link between smoking and arterial thrombosis Circulation 48 619 1973
13 Dintenfass L Elevation of blood viscosity aggregation of red cells haematocrit values and fibrinogen levels with cigarette smokers Med J Aust 1 617 1975
14 Royal College of Physicians Third Report—Smoking or Health? London 1977 Pitman Medical
15 Paetkau M E Boyd T A Winship B et al Cigarette smoking and diabetic retinopathy Diabetes 26 46 1977

Drinking water and cardiovascular disease*†

Nature has for centuries been conducting gigantic experiments as to the effect of climate of type of work of diet and of local or world wide diseases on men women and children of different races that are spread out before our very eyes for us to record and to analyze quite readily yielding information that might never be obtainable by our own experiments on man (quoted from P D White)

Man with his tremendous impact on nature has also produced unconscious experiments which are offered to the scientist as a precious material for investigation

This annotation deals with a peculiar change in a natural situation due to human intervention which was brought to our attention in the course of the Seven Countries Study This change gave us a unique opportunity to study the possible relationship between the quality of drinking water and cardiovascular disease

In the frame of this study prevalence incidence and mortality rates for IHD and hypertension were studied from 1960 to 1975 in two population group of men aged 40 to 59 years at entry living in two rural area Crevalcore and Montegiorgio respectively located in North and Central Italy At the same time the characteristics of the drinking water of the two areas were also studied

In Crevalcore the water was supplied since 1915 by an aqueduct in Montegiorgio construction started on an aqueduct able to reach all the peripheral areas of the community in 1960—the year of the beginning of our survey—and only during the next 5 to 10 years has this water supply gradually reached the most scattered farms and therefore the majority of the men belonging to the studied sample This means that most people of Montegiorgio have employed for most of their life well and other spring waters and almost all until the age of 40 years or more

The water of the wells in Montegiorgio was definitely a hard water (442 38 mg/L of $CaCO_3$) and poor in zinc The water of the aqueducts both in Crevalcore and in Montegiorgio was much lighter (respectively 214 62 and 130 65 mg/L of $CaCO_3$) and relatively richer in zinc The change of water supply from

*This work was made possible by the consent of Dr A Keys University of Minnesota, coordinator of the Seven Countries Study and by grant from the WHO G n No C3/181/86

†All water analyses were made at the Dept of Chemistry Memorial University of Newfoundland St John Canada

000_-8 03/80/040539 + 02$00 20/0

wells to aqueduct transformed Montegiorgio from 1960 to 1965 to 70—during the first 5 to 10 years of our survey—from an area supplied with a hard water poor in zinc to an area supplied with a relatively light water richer in zinc similar to the water supplied for a long time in Crevalcore

Looking at the cardiovascular conditions of ischemic and hypertensive types in the two areas from 1960 to 1975 the impression does exist that higher prevalence of IHD and hypertension and the higher incidence and mortality rate for IHD existing at the beginning of the survey in Crevalcore are being rapidly followed by a catch up period in Montegiorgio whose IHD mortality rate during the last 5 years is definitely higher than in Crevalcore The most impressive data concern cumulative IHD mortality rate which was 1 83 2.22 and 4 43% per year in Crevalcore and 0 84 1 11 and 4 17% in Montegiorgio at the three deadlines of 5 10 and 15 years respectively The increasing rates with time in both areas are due to the fact that they refer to a longitudinal study in other word to the aging effect

A similar trend indicating the tendency of Montegiorgio to catch up to Crevalcore is shown also by the mean levels of blood pressure

The information provided by these data is in agreement with the current hypothesis of the relationship between the characteristics of drinking water and cardiovascul d As a matter of fact hardness calcium and magne decreased and zinc is increased in Montegiorgio as co to Crevalcore

The available cases of morbidity and death are too provide statistical significance for IHD but only suggestive conclusions. On the other hand the d hypertension do reach statistical significance

Vittorio I
Via S
00
Alessandro L
Paolo S
Centr
Malattie Cardi
Ospedale S C
Rom

REFERENCES

1 White P D Heart disease A world problem B ll Acad Med 16 431 1940
2 Keys, A ed Coronary heart disease in seven cou Circulation 41 Suppl I p 63 1970

Of "now myocardial imaging"

The manufacturers of medical equipment too often dictate and even determine the nature of the practice of medicine and certainly the practice of cardiology Manufacturers are responsible in large part for the extreme expense of the care of the sick The use of the equipment and the cost to the patient are exponentially augmented by clinicians laboratories and hospitals Some diagnostic procedures are not only unnecessary and costly but are even hazardous—e g the treadmill Holter monitoring though not hazardous is overused as well as is the treadmill and *now* we can add to the already long list of procedures cardiac nuclear imaging the beginning of "Nuclear Cardiology I have yet to see from personal experience or from the literature where myocardial nuclear imaging has been shown to assist in any way diagnosis and management of a cardiac patient As a *research* procedure it may have application but as a *procedure* it has no real value at present and the patients should *not* be charged directly or indirect myocardial imaging until its usefulness in service to pati fully established

George E Burch
Tulane University School of Me
and Charity Hospital of L
New Orl

0002 8703/80/040540 + 01$00 10 0 © 1980 The C V M

plıfyıng cardıopulmonary resuscıtatıon rules

ıe Edıtor

rdıopulmonary resuscıtatıon (CPR) traınıng ıs beamed at ıad range of people ın all walks of lıfe ıts rules therefore ld be as sımple as possıble and they hould be easıly ımbered Most of the rules fit these mandates yet some of ı could be ımplified

ıe differences ın rate of compres ıon for one rescuer (80 s/mınute) or a team of two (60 tımes/mınute) add an dable complıcatıon The rate for adults could as well be 60) compressıons per mınute whether there ıs one rescuer or It ıs dıfficult durıng an emergency to exactly tıme the anyway Another change to facılıtate memorızıng refers ıe ratıo of compressıons to requıred breaths (15 2 for one ıer o 1 for two) Thıs could be 10 to 2 whether there ıs one ıer or a team

ıven the varıatıons ın the body sızes of vıctıms precısıon ıs nıngless and the figures provıded for CPR are only roxımatıons of what ıs optımal. It has been argued that a ıpres ıon rate of 40 would be as effectıve as one of 60

he rules can be more complex for Emergency Medıcal hnıcıans (EMTs) but for those rarely called to do CPR plıcıty and ease of recall are more ımportant considera ıs than small dıfferences ın rates.

Hans H Neumann M D
D partment of Health
On State Street
New Haven Conn 06 11

eedıng complıcatıons wıth heparın therapy

the Edıtor

The authors of Heparın therapy A randomızed prospec e study (AM HEART J 97 15 1979) state that they found ı ıncıdence of bleedıng complıcatıons to be the same ın tıents receıvıng ıntermıttent as ın those receıvıng contın us heparın therapy Thus the data regardıng the relatı e quency of bleedıng complıcatıons wıth these two regımens ntınues to be debated Some have concluded that there ıs a eater ıncıdence of bleedıng wıth ıntermıttent therapy than th contınuous admınıstratıon whıle others report no fference ın bleedıng complıcatıons between contınuous and termıttent heparın therapy One may assume after vıew that duratıon of therapy age sex and trauma are obably more ımportant determınants of hemorrha e durıng parın therapy than method of admınıstratıon What then ın one method of admınıstratıon offer over another? Perhaps e should ınvestıgate the rısk of thrombotıc complıcatıons ın latıon to the method of heparın admınıstratıon

The pharmacokınetıc studıes of heparın report that the alf lıfe of heparın ın the usual clınıcal dose ıs approxımately hours Thıs would ındıcate that the admınıstratıon of parın at 4-hour ıntervals would result ın the effectıve dose ıng equaled or exceeded for 2 of the 4 hours whıle for the tter 2 hours the heparın level would be low Therefore parın by ıntermıttent methods ıs subject to a course of peaks and valleys ındıcatıng eıther excessıve or under antıcoa gulatıon. Thıs would ımply that ıf one were to use the ıntermıttent approach the schedule of doses hould be every 2 hours as opposed to the current trend of every 4 hours but such a schedule ıs ımpractıcal Also the tıme of blood collec tıon ın relatıon to tıme of heparın admınıstratıon for proper monıtorıng becomes very crucıal when the degree of antıcoag ulatıon ıs rapıdly changıng ın relatıon to h parın half lıfe

Heparın pharmacokınetıcs ıllustrates a first-order functıon of the drug whıch ımplıes that the heparın cl arance rate ıs ındependent of pla ma concentratıons or dose levels But the dısappearance of heparın ıs more complex because ın normal subjects drug dısappearance closely hows a zero-order func tıon (the larger the dose of heparın the longer the half lıfe hence the longer the clearance) However ın the presence of thrombosıs the clearance pattern changes becomıng closer to the first order functıon Moreover ın patıents wıth pulmo nary embolısm there ıs a more rapıd clearance of heparın and a horter heparın half lıfe then wıth just venous thrombosıs alone Thus heparın kınetıcs are altered ın some way by the exıstence of thrombosıs The explanatıon appears to be un known

Therefore one could conclude that heparın gı en by contın uous ınfu ıon has advantages over the ıntermıttent method By usıng the contınuous ınfusıon method the clınıcıan ıs takıng ınto account heparın s short half lıfe ıts altered phar macokınetıcs and he ıs provıdıng clınıcally useful antıthrom botıc plasma levels and avoıdıng long perıods of eıther exces sıve or ınadequate antıcoagulatıon that may be encountered wıth the ıntermıttent method, thus avoıdıng recurrent throm botıc epısodes. Thıs appears to be partıcularly ımportant ın patıents wıth pulmonary embolısm ın that they exhıbıt ıncreased heparın clearance Also the monıtorıng of antıcoag ulatıon dose may be drawn once a day ınstead of takıng the APTT before each bolus dose of ıntermıttent ınjectıon In thıs way the clınıcıan ıs not subject to errors ımposed by the APTT resultıng from the peaks and valleys encountered wıth ıntermıttent heparın admınıstratıon

Reın Tıdeık aar R P A C
Coagulatıonıst
Jewısh Instıtute for Gerıatrıc Care
Long I land Hıll ıde Medıcal Center
271 11 76th Ave
New Hyde Park N Y 11040
Clınıcal Faculty
State Unıversıty of New York at Stony Brook
Ston B ook N Y

REFERENCES

1 Salzman E W Deykın, D et al. Management of heparın therapy Controlled prospectıve trıal, N Engl J Med 292 1046 1971
2 Glazıer R L. and Crowell, E B Randomızed prospec tıve trıal of contınuous vs ıntermıttent heparın therapy J.A.M.A 236 1365 1976
3 Mant M J, Thong K L., et al. Hemorrhagıc complıca tıons of heparın therapy Lancet 1 1133, 1977
4 Bynum L J and Wılson J E III Contınuous vs ıntermıttent heparın ın pulmonary embolısm (Abstr) Ann Rev Respır Dıs 113 148 19 6

5 Estes J W Application of the kinetics of heparin to the formulation of dosage schedules Adv Exp Med Biol 52 181 1974
6 Simon T L et al Heparin pharmacokinetics Increased requirements in pulmonary embolism Br J Haematol 39 111 1978
7 Hirsh J et al Heaprin kinetics in venous thrombosis and pulmonary embolism Circulation 53 691 1976

HL A and hypertrophic cardiomyopathy

To the Editor

We were interested in the findings of Matsumori and co workers of a lack of association of any histocompatibility antigen with hypertrophic cardiomyopathy in their study of 26 unrelated patients This contrasts with the simultaneously published results of Darsee and co workers which show a marked association with HL A B12 in Caucasoids and with HL A B5 in negroes It is notable that in the data of Matsumori and co workers both B12 and B5 were less common in the patients with hypertrophic cardiomyopathy than in the controls Possibly the different findings in the two studies just reflect the different ethnic populations studied

The finding of an association of hypertrophic cardiomyopathy with HL A A9 and HLA B7 within a family is of much lesser significance in terms of genetic linkage than would be a similar finding in unrelated subjects although the case is certainly strengthened by the finding in two separate families The authors are rightly cautious in inferring that this association implicates an immune mechanism in the etiology of hypertrophic cardiomyopathy However they cause considerable confusion when they quote two papers demonstrating that an autoimmune mechanism may be involved in the pathogenesis of some of the patients with cardiomyopathy The evidence implicating autoimmune viral or other immunological mechanisms in the pathogenesis of hypertrophic cardiomyopathy is negligible By contrast there is increasing evidence of viral and immunological mechanisms in the *development of the quite distinct disease entity congestive* cardiomyopathy The term idiopathic cardiomyopathy should be avoided because of this confusion It is essential to specify whether the cardiomyopathy is hypertrophic or congestive

As a further minor point the continuity correction for the χ test was first described by Yates not Yate It is only usual to employ this correction in fourfold tables which would not be applicable in the study of Matsumori and co workers

Colin M MacArthur MRCP
William McKenna MD
Dept of Medicine
(Clinical Cardiology)
Hammersmith Hospital and Royal
Postgraduate Medical School
Ducane Road
London W12 0HS England

REFERENCES

1 Matsumori A Hirose K Wakabayashi A Kawai C Nabeya N Sakurami T [illegible] hypertrophic cardiomyopathy Am Heart J [illegible]
2 Darsee J R Heymsfield S B and Nutt[illegible] Hypertrophic cardiomyopathy and human antigen linkage Differentiation of two forms [of hyper]trophic cardiomyopathy N Engl J Med 1979
3 Kawai C Idiopathic cardiomyopathy A st[udy on the] infectious immune theory as a cause of the d[isease] Circ J 35 765 1971
4 Kawai C and Takatsu T Clinical and ex[perimental] studies on cardiomyopathy N Engl J Med 1975
5 Cambridge G MacArthur C G C Water[son] Goodwin J F and Oakley C M Antibod[ies to Cox]sackie B viruses in congestive cardiomyopathy [Br Heart] J 41 692 1979
6 Fowles R E Bieber C P and Stinson E B [Defective] in vivo suppressor cell function in idiopathic [congestive] cardiomyopathy Circulation 59 483 1979
7 Armitage P *In* Statistical Methods in [Medical] Research Scientific Publications Oxford B[lack]well p 208

Reply

To the Editor

We thank Drs MacArthur and McKenna for th[eir comments] in our paper In our work HLA A9 and B[...] common in patients with hypertrophic cardiomyo[pathy but] there was no significant difference between pa[tients and] controls Darsee and co workers found significant [association] of HLA B5 in Negroes and HLA B12 in Cauca[soids with] hypertrophic cardiomyopathy It is well known th[at the frequen]cies of HLA antigens vary greatly among different [races and] in different populations It is conceivable that [disease] susceptibility genes are in disequilibrium with diff[erent HLA] antigens Although we found no significant a[ssociation] between HLA antigens and hypertrophic cardiom[yopathy in] the population study the occurrence of hypertrop[hic cardio]myopathy was associated with a given HLA ha[plotype in] first degree relatives of the affected family membe[rs]

Our observation suggests that a gene of the HL[A ...] some was associated with hypertrophic cardiomyop[athy in] familial occurrence but the gene was not identica[l and] did not show a very high linkage disequilibrium [with] particular HLA antigens Similar associations were [found in] the case of ragweed hay fever

There is also the problem of disease heterogene[ity; hyper]trophic cardiomyopathy may be a collection of [several] different entities so any strong association bet[ween a] susceptibility gene of the HLA system and one [of these] entities would be obscured by the fact that a ser[ies] included within the same category may not be asso[ciated with] the same disease susceptibility gene

Although further studies including studies of H[LA] DR loci are necessary to elucidate the role of the HL[A system] in the pathogenesis of hypertrophic cardiomyopath[y, studies] on HLA may be useful in the fields of nosology diag[nosis and] prognosis of hypertrophic cardiomyopathy

As Drs MacArthur and McKenna pointed out [...] our two previous papers in which autoimmune m[echanism] was suggested in the pathogenesis of cardiomyopath[y in some] of the patients It should be recalled that in th[...] when the clinical cases reported in our paper of 1[...]

ected classification or even definition of cardiomyopathy not established This was before echocardiography was :nelv available That is the reason why the term cardio pathy without mentioning the type classification hyper hic or congestive was used in that paper We of course e with the opinion that the cardiomyopathy should be ified as either hypertrophic or congestive althou h it is etimes difficult to do so even at present

n our work statistical analysis was done by the chi square using a 2 × 2 table this is usually done in an investiga to evaluate whether there is a statistically significant erence between the frequencies of HLA anti ens in ients and controls Therefore Drs MacArthur and Kenna s last comment may not be pertinent Lastly we nk them very much for correcting our pelling of Yates

Akira Matsumori M D
Chuichi Kawai M D
3rd Division Department of Internal Medicine
Faculty of Medicine
Kyoto University
54 Kawaracho Shogoin Sakyo ku
Kyoto Japan 606

FERENCES

Matsumori A Hirose K Wakabayashi A Kawai C Nabeya N Sakurami T and Tsuji K HLA in hyper trophic cardiomyopathy Igakuno-ayumi **105** 889 1978 (in Japanese)

2 Matsumori A Hirose K Wakabayashi A Kawai C Nabeya N., Sakurami, T and Tsuji, K HL A and hypertrophic cardiomyopathy AM HEART J **97** 428 1979

3 Darsee J R Heymsfield S B and Nutter D O Hypertrophic cardiomyopathy and human leukocyte antigen linkage N Engl J Med **300** 877 1979

4 Bach F H., and Rood J J The major histocompatibility complex—genetics and biology N Engl J Med **295** 806 1975

5 Singal, D P., and Blajchman M A Histocompatibility (HL-A) antigens, lymphocytotoxic antibodies and tissue antibodies in patients with juvenile diabetes Diabetes **22** 429 1973

6 Nabeya N Nagaoka K., Sakurami, T Kuno S., Tsuji K., and Nose Y HL-A in insulin-dependent diabetes mellitus in childhood in Japan J Jap Diab Soc **20** 497 1977 (in Japanese)

7 Levine B B Stember R H., and Fotino M Ragweed hay fever Genetic control and linkage to HL-A haplotype Science **178** 1201 1972

8 Kawai C Idiopathic cardiomyopathy A study of the infectious immune theory as a cause of the disease Jap Circ J **35** 765 1971

9 Kawai C., and Takatsu T Clinical and experimental studies on cardiomyopathy N Engl J Med. **293** 692 1975

Circulation of the Blood Edited by D Geniant James Balti more Maryland 1978 University Park Press 495 pages Price $59 50

This book on the circulation of blood is appropriately published on the quadricentennial of the birth of William Harvey The contributors are numerous each responsible for an aspect of the circulation The subject is well reviewed including interesting things about William Harvey cerebral cardiac and pulmonary circulations circulation and disease of the aorta action of drugs lipoproteins cardiac surgery pathology of vessels and many other problems The contributors are from all over the world mainly from England This excellent book is certainly worth owning It effectively reviews the biography of William Harvey and of the Harvey Society of New York but it also contains important papers on the circulation The papers are well written and well chosen and the subject is certainly important Surely the presentations are brief but they do reflect the opinions of the respective authors extremely well

Microcirculation Volume II Edited by Gabor Kaley and Burton M Altura editor Baltimore Maryland 1978 University Park Press 56 pages Price $52 50

This volume on microcirculation is excellent Unfortunately physician even those engaged in managing cardiovascular diseases do not understand or know the microcirculation After all it is the mall blood vessels that deliver the blood to living cells This volume is divided into four main sections e g vascular smooth muscle regulation of the microcirculatory blood flow vascular responsiveness and comparative aspects of vertebrate micro irculation The book consists of a number of papers concerned with the above subjects This is a good review f selected aspects of the microcirculation The book is highly re mmended Although complex in many parts the presentations are clear and concise

Exercise and the Heart Edited by Nanette K Wenger M D Philadelphia 19 8 F A Davis Company 246 pages

This is another timely issue of *Cardiovascular Clinics* The recent interest in exercise in diagnosis and prevention and treatment of heart disease renders this book of general interest The benefits of exercise in the prevention and management of heart disease are yet to be established and the value and need of its use in diagno is remains controversial at least in the mind f many ritical physicians physiologists and cardiologists However there are many who are fully convinced of it value in these phases of cardiology This publication briefly ummarizes very well the opinions and recommendati n f th se wh emphasi e the value of exercise in the practi e f cardi l gy her fore this book represents a good ll ti n f urrent view f the strong proponents of exer ise in the pra ti e f re li ine Physicians will find this book as well a all the f t publi ati ns of *Cardiovascular Clinic* t be an xcellent sour f seful information in cardiol gy

Fibrinolysis Edited by P J Gaffney and Balkan London 1978 Academic Press Inc London Ltd Price £ 9 50

This book contains papers presented at a symposium Istanbul Turkey during September 19 The papers the kinetics of fibrinolysins as well as their pharmacol therapeutic application This is a very good book subject Most of the contributors were from Europe of fibrinolysins in clinical practice is yet to be made s tory The practical clinical concept of the book sho cially interest physicians in general as well as cardiol vascular surgeons and other physicians This i a good cation on an important subject which reviews ver busy clinicians in one volume the problem of fibrinoly fibrinolysin therapy

Cardiovascular System Dynamics Edited by Jan Baan ham Noordergraaf and Jeff Raines Cambridge Mass The MIT Press 618 pages Price $ 0 00

This book represents the symposium held at Vall Pennsylvania during April 19 5 As with all symp publication consists of a series of selected papers subject The symposium was concerned with cardiac coronary circulation ventricular dynamics systemic tree microcirculation systemic veins pulmonary vascul control mechanisms in specific vascular bed cardiov system control theoretical methods applied to the circul experimental methods applied to the cardiovascular and cardiovascular instrumentation and computer The book consists of many papers presented by many co butors Unfortunately there were not a few papers con with the reliability of the methods employed Too freq the data are accepted as sufficiently accurate to justi physiologic interpretations when this is not so The q and answer presentations are most interesting This b summarizes very well the present concepts and prac the study of cardiovascular dynamics and theref re interest those engaged in such investigations physicians and cardiologists should appreciate thi book

The Essentials in Cardiac Pacing *An Illustrated Guide* Guy Fontaine M D Yves Grosgogeat M D Jean Welti M D and Bernard Tardieu London and Bost Martinus Nijhoff Medical Division—The Hague 80 pages

This is a brief clearly written and illustrated discuss the technic of cardiac pacing The authors in simple ter review extremely well the use of cardiac pacing The the cellular electrophysiology anatomic and phys disturbances responsible for the need of cardiac pacing equipment technic and indications are also d scussed well This is a brief 80 page effective discussi n of card pacing

ooks received

ed cal Data Transmission by Publ c Telephone Systems lited bv Hans Jurgen \ Men den and Hanjorg Just ıltımore 19‾8 Urban & Schwarzenberg 137 pa‾es Prıce 4 00

ırdiac Anesthes a Edıted b\ Joel A Kaplan M D., New ɔrk 19 9 Grune & Stratton Inc 530 pa‾e‑ Prıce $44 ‾5

ımary Care Judgments of Nurses and Physıcians Volumes II and III Bv Frank E McLaughlın Harold G John on homas A Cesa Mary M Lemons Sara J Anderson Patrıcıa Larson and Josephıne R Gıbson San Francı co 19‾8 eteran Admınıstratıon Ho pital,

Embryology and Teratology of the Heart and Great Vessels B\ C H S van Mıerop A Oppenheımer Dekkers, and C L. D C Bruıns, The Hague The Netherlands 19‾8 Martınus Nıjhoff Publısher ??4 pa es

Card ovascular Effects of Mood Alterıng Drugs B\ Barr\ Stımmel, M D New York 19/9 Raven Press 290 pages

Card o‑Vasculaıres Bv R Froment P Davıd J P Delahaye J Descotes A Gonın P Mıchaud and J Normand Parıs *New York Barcelona and Mılan* 19‾9 *Masson & Cıe* 33ɔ pages

Symposium on Dynamic Radionuclide Cardiac Studies

A symposium entitled Noninvasive regional wall motion evaluation using dynamic radionuclide cardiac studies from underlying principles to practical applications will be presented in Chicago Ill on April 18 and 19 1980 Sponsored by the University of Illinois College of Medicine Abraham Lincoln School of Medicine Department of Radiology Section of Nuclear Medicine the symposium is designed for nuclear medicine physicians cardiologists and others who desire to improve their knowledge of the latest techniques involved in these radionuclide studies The guest faculty will include speakers of national and international renown Formal lecture presentations case presentations round table discussions and workshops are featured on the agenda Registration fee for the symposium will be $100 for physicians and $50 for residents and fellows The symposium is approved for 9 hours of AMA Category 1 credit toward the Physicians Recognition Award of the AMA For further information contact University of Illinois at the Medical Center Office of Continuing Education Services 1853 W Polk St Room 144 Chicago Ill 60612 Telephone (312) 996 8025

Symposium on Clinical Trials

The First Annual Scientific Session Society for Clinical Trials and the Seventh Annual Symposium for Coordinating Clinical Trial will have a combined meeting on May 6 through 8 1980 in Philadelphia Pennsylvania The sessions will focus on the design organization management and analyses of clinical trials For further information write Christian R Klimt M D Secretary Society for Clinical Trials Inc 600 Wyndhurst Ave Baltimore Md 21210

Symposium on Radiology

A symposium entitled Radiology Today—A Multi [illegible] Symposium will be held on June 1[illegible] through 1[illegible] 19[illegible] Salzburg Austria This symposium conducted in English [illegible] bring together consultants and radiologists from Europe [illegible] the United States for a review of the most recent adva[illegible] diagnostic radiology nuclear medicine and ultra[illegible] concise review of each specialty area of diagnostic [illegible] spanning the last two years will be presented [illegible] panel discussions and informal workshops focusing on [illegible] integration of these recent advances into the patient [illegible] For further information contact Dr Martin W Donner [illegible] Johns Hopkins Hospital Baltimore Md 21205

Asian Pacific Symposium on Cardiac Pacing

The First Asian Pacific Symposium on Cardiac Pacing [illegible] be held in Jerusalem Israel from June 16 through 19 [illegible] The symposium will deal with recent advances in the [illegible] Cardiac Pacing (technology follow up rare indications [illegible] functions medico legal aspects and others) There [illegible] commercial exhibits and a special program for accomp[illegible] persons For further details write The Secretary [illegible] Asian Pacific Symposium on Cardiac Pacing P O Box [illegible] Tel Aviv Israel

American Heart Journal

May 1980 Volume 99 Number 5

ıtorıal

·crotızıng vasculıtıs coronary angııtıs and ɜ cardıologıst

eph E Parrıllo M D
thony S Faucı M D
ʼon Mass Neu York N Y and Bethesda Md.

w dıseases ın medıcıne produce as much dıag stıc and therapeutıc consternatıon as the prob n of vasculıtıs Because of ıts varıed modes of ɜsentatıon ıt ıs consıdered ın the dıfferentıal ıgnosıs of many perplexıng multısystem dıs ses However because few clınıcal tests apart ɔm bıopsıes are absolutely characterıstıc vascu ıs ıs a dıffıcult dıagnosıs to establısh and ın me cases ıs made only at autopsy The cardıol ıst may be confronted wıth the dıffıcult task of fferentıatıng the vascular stenosıs of atheroscle sıs from that of ınflammatory vasculıtıs ecent developments have made thıs dıfferentıa ɔn crıtıcal sınce a number of vasculıtıc ndromes are now responsıve to a varıety of ıerapıes The present artıcle wıll brıefly revıew cent advances that have occurred ın the classıfı ıtıon pathogenesıs and treatment of necrotız ıg vasculıtıs wıth specıal emphasıs on coronary rterıtıs

The classıfıcatıon of the dıfferent vasculıtıc yndromes has been one of the most confusıng ın ıedıcıne Thıs has been partıally true because the ategorızatıon has been done on the basıs of athologıc studıes whıch commonly bear lıttle relevance to the clınıcal presentatıon and partıal ly because there ıs much overlap among the varıous vasculıtıc syndromes and many patıents cannot be easıly placed ınto one category [1,2] Thus many authors have wrıtten about the spectrum of vasculıtıs[1] and some have argued that all vasculıtıs should be termed necrotızıng vasculı tıs and classıfıcatıon should only be used for hıstorıcal ınterest However despıte the unques tıonable overlap among the vasculıtıdes there are some well descrıbed syndromes wıth clear cut natural hıstorıes and responsıveness to dıfferent therapıes and therefore ıt ıs our opınıon that approprıate classıfıcatıon ıs worthwhıle to the clınıcıan

Table I lısts the varıous vasculıtıc syndromes, some of whıch are well defıned and others of whıch have consıderable overlap wıth one anoth er (see below) A recent revıew has delıneated the clınıcal and pathologıc presentatıons of the dıffer ent types of vasculıtıs

The vasculıtıc syndromes of most ımportance to the cardıologıst are those that prımarıly ınvolve the coronary arterıes and/or the aorta Thus Takayasu s arterıtıs the mucocutaneous lymph node syndrome (MLNS) polyarterıtıs nodosa (PAN) and vasculıtıs assocıated wıth certaın collagen vascular dıseases are the vascu lıtıc syndromes that should be very famılıar to cardıologısts Although aorta and/or coronary arterıes have been reported to be ınvolved ın temporal arterıtıs or Wegener s granulomato sıs[5] these are rare occurrences

Takayasu s arterıtıs or pulseless dısease

ʼrom th Card c Un t Massa husetts Ge ral Hosptıal a d Harvard Aedı l School Bost n Mass th Card logy D vısı n Departm nt ıf Med ın Th New Y k Hosp tal–Cornell Medıcal C nte New ʼo k N Y nd the Lab rat ry f Clını al Investıg tıon N tı nal nst tut of Allergy a d Infectıou Dıseases, Nat onal Instıtutes of ɟe lth B thesda Md

ʀec ed for publ cat on Apr 30 19 9

ʀ prınt requ sts D A tho y S F ucı, Buıldıng 10 Room 11B 13 NIAID N t onal In t tutes f H lth Bethesd Md. ʼ0ʼ05

Table 1 Classification of vasculitis

	Clinical presentation	*Pathology*	*Diagnostic workup*	*Th[illegible]*
Polyarteritis nodosa (PAN)	Multiorgan dysfunction especially of kidney gastrointestinal tract heart and peripheral nervous system Commonly accompanied by generalized systemic complaints—fever weight loss, arthralgias/myalgias. In fantile form may overlap with MLNS	Necrotizing vasculitis with fibrinoid necrosis of small and medium sized muscular arteries Lung and spleen characteristically spared Microaneurysms characteristic	Arteriography Organ biopsy Lmked in significant number of cases (~30%) to hepatitis-B infection	Cortico[illegible] Cyto[illegible] therap[illegible]
Allergic granulomatosis (Churg and Strauss)	Previous allergic history usually asthma eosinophilia pulmonary infiltrates also involves heart kidney GI tract and peripheral nerves	Necrotizing vasculitis with eosinophils and granuloma formation of small and medium-sized muscular arteries as well as capillaries and venules	Arteriography Biopsy (especially of lung)	Cortico[illegible] Cyto[illegible] agents
Hypersensitivity vasculitis primary or secondary	Most confusing and heterogeneous category of vasculitis Most commonly involved organ is skin with palpable purpura, urticaria or wide variety of skin lesions. May involve only skin or may involve many organs to variable degree—kidney heart GI tract Has been linked to drug ingestion, certain bacterial infections (*Streptococcal*) or may occur without precipitating cause	Necrotizing vasculitis of small vessels especially postcapillary venules with neutrophil infiltration nuclear debris (leukocytoclastic vasculitis) fibrinoid necrosis and erythrocyte extravasation	Biopsy	Withdraw[illegible] of[illegible] [illegible]
Wegener's granulomatosis	Sinusitis, pulmonary nodules and glomerulonephritis	Necrotizing granulomatous vasculitis of medium and small vessels of upper and lower respiratory tract necrotizing glomerulonephritis	Biopsy of involved organs	Cyto[illegible] [illegible]
Temporal arteritis	Disease of elderly Fever polymyalgia rheumatica headache visual difficulty	Giant cell panarteritis of arteries of carotid system (especially temporal artery)	Temporal artery biopsy	Cortico[illegible] [illegible]
Takayasu s arteritis	Young women most commonly affected Early disease produces generalized systemic symptoms. Late disease symptoms related to large vessel (subclavian carotid) occlusion	Granulomatous panarteritis particularly of aortic arch and large branches also may affect pulmonary artery Occasional giant cells	Aortography Biopsy difficult because involved vessels inaccessible	Cortico[illegible] [illegible]
Mucocutaneous lymph node syndrome (MLNS)	Infants and young children Fever cervical adenitis conjunctivitis erythematosus–desquamating rash of skin and mucous membranes. 1 2% die due to coronary arteritis	Coronary arteritis most common with aneurysm formation and myocardial infarction due to coronary occlusion	Coronary angiography	[illegible]
Buerger's disease	Seen largely in young adult males Peripheral arterial insufficiency in cigarette smokers	Intermediate and small arteries of upper and lower extremities. Thrombus formation with polymorphonuclear infiltration	Arteriography	Absten[illegible] [illegible]
Arteritis of rheumatic fever	Fulminant a ute rheumatic fever	Associated with Aschoff bodies Small arteries of heart and lung most involved	Workup for acute rheumatic fever	[illegible]

argely a disease of young women with predilection for the aortic arch and its major branches as well as relatively frequent (up to 50 per cent in series) involvement of the pulmonary arteries [15] This vasculitis appears to have two broad clinical presentations—one characterized by generalized malaise headache paresthesias and generalized signs of active inflammation The second presentation is due to locally occluded vessels and subsequent ischemia of arms legs or brain [10, 11] A recent report has related four complications of the disease—retinopathy secondary hypertension aortic regurgitation or aneurysm formation—to ultimate prognosis All of the patients who died of Takayasu s arteritis had at least one and usually two or more of these complications Establishing a diagnosis can often be difficult since the involved vessels are often large and relatively inaccessible to biopsy Diagnosis usually depends upon arteriographic demonstration of tubular vessel narrowing in a clinical setting where atherosclerosis is unlikely Corticosteroids are efficacious in ameliorating the general systemic symptoms and signs of the disease and some authors have reported return of flow to previously pulseless extremities[11] however results of corticosteroid trials have been variable especially when extremity or organ ischemia has been the major disease manifestation Careful clinical therapeutic trials will be needed to determine whether corticosteroids (or cytotoxic agents) will be capable of preventing the complications of the disease which have been related to a poor prognosis Surgical vascular reconstruction and aortic valve replacement for aortic regurgitation have been successfully employed in a small number of cases

The MLNS or Kawasaki s disease is an extraordinarily interesting form of vasculitis originally recognized in Japan only 10 years ago MLNS has considerable import to cardiologists because of its peculiar predilection for coronary vessels Largely a disease of infants and young children the syndrome manifests itself as fever bilateral conjunctival infection erythematous scaling rash of the skin of the extremities involvement of the oral mucous membranes and non suppurative swelling of the cervical lymph nodes Other less characteristic associated acute symptoms and signs have been myocarditis or pericarditis diarrhea arthritis proteinuria and signs of inflammation (increased sedimentation rate C reactive protein but negative anti streptolysin O) The prognosis of this acute syndrome is usually good However 1 per cent to 2 per cent of patients will die suddenly commonly in the recovery phase of the acute illness At autopsy the cause of death is coronary arteritis commonly with aneurysm formation and coronary thrombosis with extensive myocardial infarction [16]

A recent study has ominously reported abnormalities of angiographically determined coronary artery anatomy in 12 of 20 patients during and up to 4 years after acute MLNS [19] Seven of the 20 had coronary artery aneurysms Two patients showed regression of the coronary aneurysms at subsequent angiography and one patient developed mitral regurgitation as a result of papillary muscle dysfunction Another report found electrocardiographic abnormalities in 40 to 54 cases (74 per cent) with MLNS and angiography showed abnormalities in 14 of 17 (82 per cent) patients studied Of the total of 72 patients in this report eight developed mitral regurgitation and/or progressive congestive heart failure (CHF) Three patients died with progressive CHF and a fourth patient died suddenly These studies suggest that involvement of the coronary arteries may be much more frequent than the original autopsy studies suggested Apparently in some patients the coronary arteritis can spontaneously remit in other patients the arteritis causes aneurysm formation and/or thrombosis The natural history of asymptomatic coronary artery involvement remains unclear at present and will require careful follow up of these patients

Ventricular function in MLNS patients with coronary involvement can show segmental contraction abnormalities secondary to myocardial infarction or generalized hypokinesia presumably secondary to myocarditis Two dimensional echocardiography has been recently employed to non invasively visualize coronary aneurysms in patients with MLNS

Pathologically essentially all patients dying of MLNS showed active and healing coronary arteritis with intimal proliferation fibrinoid necrosis and multiple aneurysms Although arteritis of other vessels can be seen the coronaries are by far the most frequently involved In addition the hearts commonly demonstrated myocarditis and pericarditis that could not be ascribed to ische

mia Because of the histopathologic similarity of this MLNS coronary arteritis to that of infantile PAN some authors have concluded that they are the same disease

A clinical approach to the management and therapy of this disease is very difficult because only a small percentage of those stricken with the acute syndrome will develop clinical heart disease and an even smaller percentage will die from the disease The recent report of coronary aneurysm visualization of non invasive cross sectional echocardiography[21] provides a method of evaluating every patient with MLNS to assess the possibility of coronary involvement However, the sensitivity of this procedure still needs to be determined Furthermore the prognostic significance of asymptomatic aneurysms is unknown and an effective mode of treatment is also not proven. Although corticosteroids may be helpful in symptomatically improving the acute syndrome their effect on the coronary arteritis is unknown Cytotoxic agents are untried and are difficult to employ in infants and young children A number of successful coronary artery bypass operations have been reported in patients with coronary aneurysms but the proper indications for this operation in MLNS and the long term effects are presently unknown

Classic PAN is a systemic necrotizing vasculitis of small and medium sized muscular arteries of many organs but most commonly involving arteries in the kidney gastrointestinal tract, heart and peripheral nervous system Histopathologically muscular arteries are involved by a panarteritis with neutrophil (later mononuclear) infiltration fibrinoid necrosis and characteristic aneurysm formation As originally described and classified PAN did not involve pulmonary vasculature and eosinophilia and an allergic history were uncommon In contradistinction classic allergic granulomatosis reported by Churg and Strauss is a vasculitis of muscular arteries as well as small arterioles capillaries and venules Lung involvement is the rule rather than the exception Most patients have a preceding history of asthma and eosinophilia and granulomatous reactivity is common Many patients with systemic necrotizing vasculitis do not classify into either of these disorders and are considered to have an "overlap syndrome—commonly with some features of hypersensitivity vasculitis (see Table I) as well Because many patients (in some series the majority) fall into this overlap syndrome attempts at strict classification of these types of vasculitis are often not possible and this entire group would best be considered under the broad category of severe systemic necrotizing vasculitis

Coronary arteritis is a frequent finding in patients with classic PAN allergic granulomatosis, or the overlap syndrome In a review of 66 cases of polyarteritis nodosa (defined as a severe generalized necrotizing angiitis) autopsied over a 32 year period coronary arteritis was found in 62 per cent and usually involved both large muscular arteries and smaller vessels Myocardial infarction was found also in 62 per cent of these patients and was acute in 9 per cent of those with infarcts CHF was a common problem in these patients probably secondary to myocardial infarction and hypertensive heart disease CHF was felt to be the cause of death in 44 per cent of the 66 patients demonstrating that cardiac involvement in systemic vasculitis is a frequent (in this series the most frequent) cause of death

Interestingly, myocardial infarction was diagnosed clinically in only three patients, although it was found at autopsy in some 41 patients CHF was the most common clinical presentation of myocardial infarction Thus heart failure in the setting of generalized vasculitis should make one suspect that coronary arteritis may be producing silent myocardial infarction In this series myocarditis was found in only 3 per cent of cases and was considered to be clinically insignificant

The natural history of necrotizing vasculitis of the polyarteritis type was that of progressive multisystem organ dysfunction usually leading to death In retrospective studies corticosteroid therapy has been associated with an improved 5-year survival from 13 per cent in untreated patients to 48 per cent in those treated with corticosteroids[33] Because of our success at NIH in treating patients with Wegener's granulomatosis with the cytotoxic agent cyclophosphamide and because of data suggesting that corticosteroids alone are ineffective in over one half of patients with PAN, patients with necrotizing vasculitis of PAN type at NIH have been treated with cyclophosphamide usually together with corticosteroids immediately upon diagnosis Seven of 11 patients have achieved long term remissions and most of the failures were

patients whose disease was far advanced with considerable end organ damage Thus it seems that cytotoxic agents with or without corticosteroids are more efficacious than corticosteroids alone in treating severe necrotizing vasculitis of the PAN group

Although almost all of the collagen vascular diseases have been associated with some form of vasculitis the three collagen diseases most commonly complicated by systemic vasculitis are acute rheumatic fever rheumatoid arthritis and systemic lupus erythematosus The coronary arteritis of acute rheumatic fever is usually seen in severe episodes of this disease where diagnosis by Jones criteria is relatively obvious [3] However the coronary arteritis of rheumatoid arthritis may be very difficult to diagnose A number of series have shown that coronary arteritis may be seen in as many as one fifth of patients autopsied with rheumatoid arthritis usually as part of a widespread diffuse vasculitis of many organs [3,-3] In rheumatoid arthritis a small vessel hypersensitivity vasculitis is more commonly seen than a large vessel PAN like vasculitis the latter occurring predominantly in patients with seropositive erosive arthritis subcutaneous nodules and episcleritis Although some original reports [3, 3] suggested that corticosteroid therapy precipitated or worsened the arteritis of rheumatoid arthritis more recent studies have shown that this is probably not correct Rather vasculitis is a manifestation of severe rheumatoid arthritis which is more likely to be treated with corticosteroids In most instances the coronary arteritis of rheumatoid arthritis does not produce clinical cardiac dysfunction However CHF myocardial infarction and sudden death have been reported [39] Treatment of the vasculitis of rheumatoid arthritis has been generally directed at the underlying disease usually with corticosteroids and/or cytotoxic agents [1]

Systemic lupus erythematosus can affect the heart in a number of ways—myocarditis endocarditis pericarditis aortic insufficiency hypertensive heart disease (frequently due to renal insufficiency) and coronary arteritis [0] Coronary arteritis induced myocardial infarction has been reported but is considered to be rare [3]

A very intriguing and important finding is markedly accelerated atherosclerotic coronary artery disease (as well as other vessels) in patients with systemic lupus erythematosus [4, 5] Buckley and Roberts argue that this premature atherosclerosis was secondary to the corticosteroid therapy However their data are also just as consistent with the possibility that corticosteroids suppressed the extracardiac manifestations of systemic lupus erythematosus and allowed their patients to live long enough to develop diffuse atherosclerosis associated with factors directly or indirectly related to the underlying disease [6, 47]

Viral induced vascular injury either directly or through the immune response has also been postulated to predispose one to accelerated atherogenesis [4] A recently developed animal model has demonstrated that viral infection can predispose certain animals to develop premature atherosclerosis [9] Thus the vasculitis of systemic lupus erythematosus as well as any generalized vasculitis represents a double threat first the acute vasculitis may produce enough vessel injury to cause acute inflammatory narrowing and tissue ischemia second the arterial injury serves as a nidus for accelerated atherosclerosis which further narrows vessels resulting in premature arteriosclerotic occlusions Some authors have suggested that inflammatory vascular changes may underlie much of the premature atherosclerosis seen in young patients

Pathogenesis and etiology of vasculitis

The pathogenesis and etiology of most human vasculitis is not completely understood However experimental animal models of immune complex vasculitis and chronic viral infection combined with recent demonstrations of viral infections associated with human vasculitis have provided strong evidence for the importance of immune mechanisms and viral infection in human arteritis Most of human vasculitis is probably mediated via intravascular immune complex formation in antigen excess and entrapment of these complexes along the basement membrane of vessel walls with activation of complement components Defective reticuloendothelial clearance of complexes may be important in pathogenesis Complement derived chemotactic factors promote accumulation of polymorphonuclear leukocytes which release lysosomal enzymes and damage vessel walls From experimental models it would appear that certain animals (perhaps humans) are genetically predisposed to produce the type of immune response that will culminate in inflammatory vascular damage [3] Other mech

anisms of immune damage (e g cellular or IgE mediated) have been postulated to produce vasculitis but the evidence is inconclusive [1]

The source of antigenic stimulation in human vasculitis is quite variable In some cases exposure to a drug or a microbial infection appears to clearly precipitate a bout of vasculitis Thus sulfonamide ingestion and streptococcal infections [4, 5] have been associated with hypersensitivity type vasculitis The association of amphetamine abuse with systemic vasculitis [6] may be another example of drug induced immune complex vasculitis in humans

Chronic viral infection has been shown to produce immune complex mediated vasculitis in a number of animal models In humans hepatitis B infection has been reported in up to 40 per cent of cases of necrotizing vasculitis Circulating immune complexes and vessel wall deposition of hepatitis B antigen immunoglobulins and complement have been demonstrated in a number of these patients The recent report of serous otitis media associated with systemic necrotizing vasculitis raises the possibility that an as yet unidentified microorganism probably viral causes serous otitis media and precipitates vasculitis [1]

The MLNS has many features of a serum sickness like immune complex reaction (rash fever arthralgias lymphadenopathy) and a subset of patients (as in experimental models of immune complex disease) appear to develop the serious complication of arteritis usually of the coronary vessels The fact that coronary arteritis is commonly found in the recovery phase of the acute syndrome suggests that the immune response rather than the actual infection may be responsible for the arteritis Although rickettsia like organisms have been reported to be demonstrable in certain tissues in this disease these reports have not yet been confirmed The recent report of elevated IgE levels in MLNS is of particular interest One could speculate that a rickettsial (or viral infection) is responsible for the acute syndrome of rash fever etc of MLNS Some patients might have a genetic predisposition to produce an immune response that results in large amounts of circulating immune complexes in antigen excess These complexes could deposit in coronary vessel perhap facilitated by IgE mediated reactions causing increased vessel permeability [5] These immune complexes might then produce an inflammatory resp_ vessel damage aneurysm formation and sub quent coronary occlusion

In systemic lupus erythematosus rheuma arthritis and essential mixed cryoglobul_ immune complexes have been shown to med_ many of the disease manifestations [1, 2] The f that signs of active disease (circulating imm_ complexes low serum complement levels cr globulinemia or high titers of rheumatoid fac_ are commonly associated with vasculitis le further support to the concept that a immune processes mediate vessel damage many human vasculitides [1]

Conclusion

In conclusion it is important for the cardic gist to be familiar with the clinical syndromes of vasculitis so that the appropriate diagnostic te are performed Vessel inflammation can b mimic atherosclerotic occlusive disease and pr dispose to premature atherosclero is P_ advances in understanding certain of the p_ physiologic mechanisms of some of the se necrotizing vasculitides suggest that most f_ of vasculitis are probably capable of bei g _ pressed by an appropriate immunosuppres therapeutic regimen Therapy is most effe t against active progressive early vasculitis O end organ damage has occurred reversibi t suppression with corticosteroids and/or cyto agents is less effective Thus early diagnosis _ paramount importance to the control of th diseases Tissue biopsy and/or angiogr_ should be performed early to establish a diag_ so that appropriate therapy can be in before severe end organ damage has ensued

REFERENCES

1 Fauci, A S Haynes B F and Katz, P The spec_ vasculitis Clinical pathologic immunol_ and the_ peutic considerations (Part 1) Ann Intern Med 89 19 8
2 Christian C L and Sergent J S Vasculitis syndr_ Clinical and experim ntal models, Am J Med 61 19 6
3 Zeek P M Periarteritis nodosa A cr ical rev_ J Clin Pathol 22 77 19_
4 Cooke W T, Choake P C P Covan A D T Colbeck J C Temporal arteritis A genera_ and se_ disease Q J Med 15 4 194_
5 Fauci A S and Wolff S M Wegener s gra_ Studies in eighteen patients and a review of the l_ ture Medicine 52 35 1973
6 Wolff S M, Fauci A S Horn R C and Dale D C

Wegener s granulomatosis Ann Intern Med 81 513, 1974
7 Nakao K Ikeda M Kimata S Nutani H Miyahara M Ishimi Z Hashiba K Takeda Y Ozawa T Matsushita S and Kuramochi M Takayasu s arteritis Clinical report of eighty four cases and immunological studies of seven cases Circulation 35 1141 1967
8 McKusick, V A A form of vascular disease relatively frequent in the Orient Am Heart J 63 57 1962
9 Vinijchaikul, K Primary arteritis of the aorta and its main branches (Takayasu s arteriopathy) A clinicopathological autopsy study of eight cases, Am J Med 43 15 1967
10 Lupi Herrera E Sánchez Torres G Marcushamer J Mispireta J., Horowitz, S and Vela J E Takayasu s arteritis Clinical study of 107 cases Am Heart J 93 94 1977
11 Fraga, A Mintz G Valle L., and Flores-Izguierdo G Takayasu s arteritis Frequency of systemic manifestations (study of 22 patients) and favorable response to maintenance steroid therapy with adrenocorticosteroids (12 patients) Arthritis Rheum 15 617 1972
12. Ishikawa K Natural history and classification of occlusive thromboaortopathy (Takayasu s disease) Circulation 57 27 1978
13 Austen W G and Shaw R S Surgical treatment of pulseless (Takayasu s disease) N Engl J Med. 270 1228 1963
14 Aldasoro G E Escobar S C Cardova L Derung H Frias A. and Dominguez, F Hypogastric carotid bypass for Takayasu s disease Int Surg 61 168 19 6
15 Honig H S Weintraub A M Gomes M N Hufnagel C A and Roberts W C Severe aortic regurgitation secondary to idiopathic aortitis, Am J Med 63 623 1977
16 Kawasaki, T Kosaki F Okawa S Shigematsu I and Yanagawa H A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan Pediatrics 54 271 1974
17 Morens D M and O'Brien R. J Kawasaki disease in the United States (Editorial) J Infect. Dis 137 91 1978
18. Melish M E Hicks R M and Larson E J Mucocutaneous lymph node syndrome in the United States Am J Dis Child 130 599 1976
19 Kato H Koike S Yamamoto M and Yano E Coronary aneurysms in infants and young children with acute febrile mucocutaneous lymph node syndrome J Pediatr 86 89? 1975
20 Ononchi Z Tomizawa N Goto M Nakata, K Fukuda M and Goto M Cardiac involvement and prognosis in acute mucocutaneous lymph node syndrome Chest 68 297 1975
21 Takao A Kasakawa S Isamu H Ando M., and Assi T Cardiovascular lesions of mucocutaneous lymph node syndrome Circulation 50(Suppl. III) III 39 1974.
22 Kegel S M Dorsey T J Roweu M and Taylor W M Cardiac death in mucocutaneous lymph node syndromes, Am J Cardiol. 40 282 1977
23 Kitamura S Kawashima Y Kawachi, K Fujino M Kozuka T Fujita T and Manabe H Left ventricular function in patients with coronary arteritis due to acute febrile mucocutaneous lymph node syndrome or related diseases Am J Cardiol 40 156 1977
24 Yoshikawa J Yanagihara K Owaki, T., Kato H Takogi Y Okumachi, F Fukaya T., Tomita Y and Baba K Cross-sectional echocardiographic diagnoses of coronary artery aneurysms in patients with mucocutaneous lymph node syndromes Circulation 59 133 1979
25 Tanaka, N., Sekimoto K., and Naoe, S Kawasaki disease Relationship with infantile polyarteritis nodosa Arch Pathol. Lab Med. 100 81 1976
26 Radford D J., Sondheimer H M Williams, G J and Fowler R S Mucocutaneous lymph node syndrome with coronary artery aneurysm Am J Dis. Child. 130 596 1976
27 Landing, B H and Larson E J Are infantile periarteritis nodosa with coronary artery involvement and fatal mucocutaneous lymph node syndrome the same? Comparison of 20 patients from North America with patients from Hawaii and Japan Pediatrics 59 651 1977
28 Glanz G Bittner S J Berman, M A., Dolan T F., and Talner N S Regression of coronary artery aneruysms in infantile polyarteritis nodosa N Engl. J Med 294 939 1976
29 Kitamura S., Kawashima Y Fujita, T., Mori, T Oyama, C., Fujino M Kozuka T N Shizaki, K and Manabe H Aortocoronary bypass grafting in a child with coronary artery obstruction due to mococutaneous lymph node syndrome Circulation 53 1035 1976
30 Kussmaul, A. and Maier K. Uber eine bischer nicht beschreibene eigenthumbliche Arterienerkrankuny (Periarteritis nodosa) die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellahmung einhergeht, Dtsch. Arch. Klin. Med 1 484 1866
31. Churg J and Strauss, L. Allergic granulomatosis allergic angiitis and periarteritis nodosa Am J Pathol. 27 277 1951
32. Holsinger D R Osmundson P J and Edwards J E The heart in periarteritis nodosa Circulation 25 610 1962.
33. Frohnert, P O and Sheps S G Long term follow up study of periarteritis nodosa Am J Med 43 8 1967
34 Stollerman, G H Rheumatic Fever and Streptococcal Infection New York 1975 Grune & Stratton, Inc., pp 134-135
35 Kemper J W., Baggenstoss A. H., and Slocumb C H The relationship of therapy with cortisone to the incidence of vascular lesion in rheumatoid arthritis. Ann. Intern. Med 46 831 1957
36. Schmid, F R Cooper N S Ziff M., and McEwen C Arteritis in rheumatoid arthritis, Am J Med. 30 56, 1961
37 Mongan E S Cass, R. M Jacox R. F., and Vaughan, J H A study of the relation of seronegative and seropositive rheumatoid arthritis to each other and to necrotizing vasculitis Am J Med 47 23 1969
38 Sokoloff L. Cardiac involvement in rheumatoid arthritis and allied disorders Current concepts, Mod. Concepts Cardiovasc Dis. 33 837 1964
39 Swezey R L. Myocardial infarction due to rheumatoid arteritis. An antemortem diagnosis, J.A.M.A. 199 855 1967
40 Estes D., and Christian C L. The natural history of systemic lupus erythematosus by prospective analysis, Medicine 50 85 1971
41 Decker J L., Steinberg A D Gershwin M E., Seaman W E Klippel, J H Plotz P H and Paget, S A Systemic lupus erythematosus Contrasts and comparisons, Ann. Intern Med 82 391 1975
42. Bonfiglio T A., Botti, R. E and Hagstrom J W C Coronary arteritis occlusion and myocardial infarction due to lupus erythematosus, Am. Heart J 83 153, 1972.
43. Shearn M A. The heart in systemic lupus erythematosus, Am. Heart J 58 452 1959
44 Tsakraklides, V G., Blieden L. C and Edwards J E

Coronary atherosclerosis and myocardial infarction associated with systemic lupus erythematosus AM. HEART J 87 637 1974
45 Buckley B H., and Roberts, R C The heart in systemic lupus erythematosus and the changes induced in it by corticosteroid therapy A study of 36 necropsy patients, Am J Med. 58 243 1975
46 Minick, C R Alonso D R and Rankin L. Role of immunologic arterial injury in atherogenesis Thromb Haemostas. 39 304 1978
47 Minick, C R Murphy G E and Campbell W G Experimental induction of athero arteriosclerosis by the synergy of allergic injury to arteries and lipid rich diet I Effect of repeated injections to horse serum in rabbits fed a dietary cholesterol supplement J Exp Med. 124 635 1966
48 Burch, G E Viruses and atherosclerosis (Editorial) AM HEART J 87 407 1974.
49 Fabricant C G., Fabricant, J., Litrenta, M N., and Runick, C R Virus-induced atherosclerosis, J Exp Med. 148 335 1978.
50 Saphir O., and Gore I Evidence for an inflammatory basis of coronary atherosclerosis in the young Arch. Pathol. 49 418 1950
51 Cochrane C G and Koffler D Immune complex disease in experimental animals and man, *in* Advances in Immunology vol. 16 edited by Dixon F J and Kunkel, H. G., New York, 1973 Academic Press Inc., pp 185-264
52. Frank, M M., Hamburger M I. Lawley T J., Kimberly R P., and Plotz, P H Defective reticuloendothelial system Fc receptor function in systemic lupus erythematosus N Engl. J Med. 300 518 1979
53 Oldstone M B A., Dixon F J., Mitchell, G F., and McDevitt H O Histocompatibility linked genetic control of disease susceptibility Murine lymphocytic choriomeningitis virus infection J Exp Med. 137 1201 1973
54 Fardham C C Epstein F H., Huffins, W D., and Harrington J T Polyarteritis and acute post coccal glomerulonephritis Ann. Intern. Med 1964
55 Sams W M., Thorne E G Small, P Mass McIntosh R M., and Stanford R. E Leukocytoclastic vasculitis, Arch. Dermatol. 112 219 1976
56 Citron B P., Halpern M., McCarron M Lundberg D., McCormick R Pincus I J Tatter D and back B J Necrotizing angiitis associated with drug abuse N Engl. J Med 283 1003 1970
57 Oldstone M. B A., and Dixon F J Pathogenesis of chronic disease associated with persistent lymphocytic choriomeningitis immune response to tissue in chronic lymphocytic choriomeningitis disease, J Exp Med 131 1 1970
58 Porter D D Larsen A. E., and Porter H. G pathogenesis of Aleutian disease of mink, Am. J Pathol 71 331 1973
59 Gocke D J., Hsu K Morgan, C Bombardieri Lockshin, M., and Christian, C L. Association between polyarteritis and Australia antigen Lancet 1970
60 Sergent J S Lockshin M D Christian, C L Gocke, D J Vasculitis with hepatitis-B antigenemia Long term observations in nine patients, Medicine 1976
61 Sergent J S., and Christian, C L. Necrotizing vasculitis after acute serous otitis media, Ann. Intern. Med 1974
62. Hamashima, Y Kishi K., and Tasaka, K. Rickettsia like bodies in infantile acute febrile mucocutaneous syndrome (Letter) Lancet 2 42, 1975
63 Kusakawa S and Heiner D C. Elevated levels of immunoglobulin E in the acute febrile mucocutaneous lymph node syndrome Pediatr Res. 10 108, 1976
64 Henson, P M Interaction of cells with immune complexes Adherence release of constituents and injury J Exp Med. 134 114 1971

May 1980 Vol 99

Correlation of the location of coronary arterial spasm with the lead distribution of ST segment elevation during variant angina

Rex N MacAlpin M D *
Los Angeles Calif

Angina pectoris associated with transient ST segment elevation (variant angina) is usually due to localized transmural myocardial ischemia resulting from temporary severe obstruction or occlusion of a major coronary artery due to vasoconstriction or spasm of an epicardial portion of that vessel [1] Localization of the involved coronary artery helps to clarify the pathophysiology of a patient s attacks and to plan appropriate therapy Coronary arteriography during a spontaneous or provoked attack of angina is the most reliable way to accomplish this but is not feasible in every case A multilead electrocardiogram (ECG) made during an attack although not always easy to obtain exposes the patient to less expense risk and discomfort than does coronary arteriography and is frequently available before the latter procedure is undertaken Although it seems likely that a multilead ECG made during an attack would be very helpful in localizing the involved coronary artery or arteries this supposition has never been critically examined

Materials and methods

No one investigative group of physicians by itself has enough complete observations on variant angina patients in order to address this problem In my own observations of 62 variant angina patients there were only eight patients for whom all of the following data were available (1) a multilead ECG recorded during the course of an attack of variant angina a full 12 lead ECG was not required providing that sufficient leads were present to generally localize the ST elevation to the inferior anterior or lateral distributions (2) a multilead ECG in the absence of angina recorded before or after the anginal attack for comparison (3) coronary arteriography during an attack of myocardial ischemia produced by documented acute coronary artery obstruction or occlusion resulting from severe coronary artery vasoconstriction or spasm involving only one major coronary artery The multilead ECG need not have been recorded at the same time as the arteriogram providing that there was some evidence that myocardial ischemia was present during the episode of coronary vasoconstriction (angina or ECG changes) This episode of myocardial ischemia could be spontaneous or iatrogenically provoked (e g., by ergonovine maleate methacholine or exercise)

From a review of over 1 700 cases of variant angina publishhed in the literature an additional 102 patients were selected for whom the above data were available [2-42]

Data from this combined group of 110 patients (group A) was used to study the correlation between the location of the coronary arterial constriction or spasm during myocardial ischemia and the distribution of acute ST segment elevation on the ECG

Another group of 20 cases from my own patients and 94 others from the published literature was selected to form a group of 114 patients

From the Department f Medicin UCLA School of Medicine Los Angeles Calif

Supported in part by a grant from Marion Laboratories, Kansas City Mo

Recei ed f r publication Aug 6 1979

Accepted for publication N v 27 1979

Reprint requests Rex MacAlpin M.D Dept. of Medicin UCLA Cent for the He lth Sciences, Los Angeles, Calif 90024

*Professor of Medicin /C rdiology Dept. of Medicine, UCLA School of Medicine

0002-8703/80/050555 + 10$01 00/0 © 1980 The C V Mosby Co

Table I Lead distribution of ST segment changes observed during variant angina related of coronary arterial spasm

ECG lead	Right CA spasm (n = 57) No of cases showing: ST elevation	ST depression	No ST change	Anterior descending CA spasm (n = 39) No of cases showing: ST elevation	ST depression	No ST change	Circumflex spasm (n = No of cases sh: ST elevation	ST depress
1	0	12	43	9	0	4	0	2
2	55	0	1	1	6	5	13	1†
3	55	0	1	0	5	6	17	0
aV_R	0	2	53	0	0	10	0	3
aV_L	0	16	39	11	0	2	0	5
aV_F	56	0	1	0	6	5	12	0
V	2	11	6	21	0	13	0	4
V	0	10	7	35	0	1	0	3
V	0	11	8	36	0	1	0	2
V	0	11	8	32	0	5	0	1
V	3	8	9	17	2	15	5	1
V	5	5	9	9	2	22	4	0

*The number of total cases showing either ST elevation, depression or no change in any lead is less than the total number of patient because not all patients had all leads recorded during an attack. A 0 means that no patient in that group in whom that finding in that lead.

†Findings in a case of CA spasm limited to a marginal branch of the circumflex CA ST elevation was limited to Leads V and V

Abbreviation CA = coronary artery

(group B) in whom relatively more complete ECG data were available before and during attacks of variant angina in order to establish in what leads the greatest degree of ST segment elevation was observed All of these patients had had coronary arteriography but demonstration of coronary artery spasm was not required [7, 9, 11, 17, 22, 25, 28, 31, 34, 35, 38, 86]

I shall use the term coronary arterial spasm in this article to refer to the production of acute transient obstruction (or worsening of a pre existing organic obstruction) in an epicardial coronary artery as the result of contraction of the vascular smooth muscle in its wall. The reader should be advised that this is a convenience and not be misled into thinking that all coronary arterial spasm" implies hyperreactivity of the vascular smooth muscle In the presence of important thickening of the vascular wall or of pliable organic stenosis normal amounts of smooth muscle contraction can produce severe obstruction or complete occlusion

Results

Location of ST segment shift in relation to coronary spasm Coronary arterial spasm causing either ischemic ST segment shift or angina or both produced complete occlusion of the vessel in 54 cases produced 90% to 99% diamete in 36 cases produced 80% to 89% stenosi cases and resulted in 70% to 79% stenosi cases (severity of spasm caused stenosis specified in 10 cases)

In Table I are shown the data relating distribution of ST segment changes dur ant angina to the observed site of c arterial spasm in the 110 patients in whor was actually observed in only one vessel A) Transient ST segment elevation in Le and aV_F was *almost* always present attacks in patients demonstrated to have spastic obstruction of the right coronary One patient of mine had complete spastic sion of the proximal part of a dominant coronary artery (Fig 1) at which time he showed only upright peaking of a prev inverted T wave in Lead aV_F and ST se depression in Lead V_1 (Fig. 2) there w significant ST segment elevation despite absence of visible collateral circulation on quent left coronary visualization after subse of the attack This patient was never see manifest significant ST segment elevati a 12 lead ECG during spontaneous anginal tacks

On the other hand ST segment elevatio

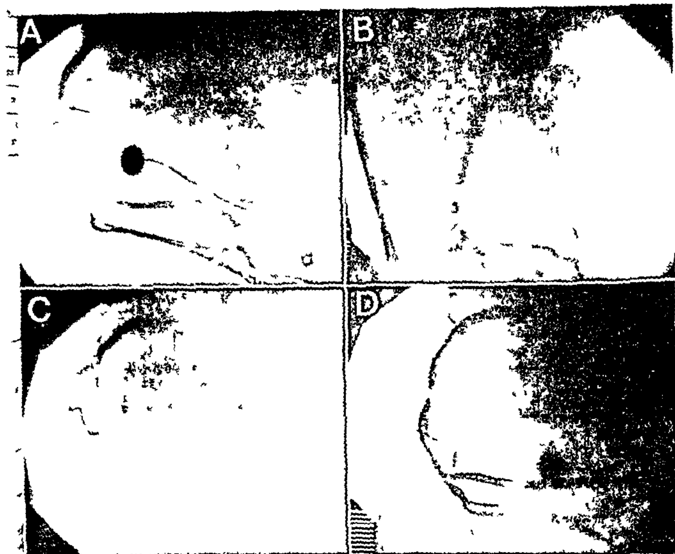


Fig 1 Selective arteriograms of the right coronary artery in a 51 year-old woman with clinical symptoms of variant angina *A* Left anterior oblique (LAO) projection prior to onset of symptoms demonstrates an 80% stenosis *(arrow)* in the anterior portion of the vessel with rapid and complete opacification of the distal vessel *B* Right anterior oblique view in the absence of symptoms hows the same stenosis which here appears only 60% *C* LAO view durin the h ight of a spontaneous anginal attack shows complete occlusion of the vessel at the site of previous stenosis The distal vessel is not visualized ECG at this time did not show ST segment elevation *(See fig 2)* *D* LAO projection 3 minutes after relief of angina by sublingual nitroglycerin The vessel is again patent but the organic steno is persi ts

Leads 2 3 and aV_F was not *specific* for acute right coronary artery obstruction since it also occurred in almost all cases of severe circumflex coronary artery spasm as well Whereas a dominant left coronary artery circulation was present in most of these cases it was not a necessity in order for circumflex spasm to produce ST elevation in inferior leads When ST segment elevation was present in inferior leads as the result of right or circumflex coronary artery spasm it was almost always present simultaneously in Leads 2 3 and aV_F

ST segment elevation in lateral precordial leads (V and V) concomitant with inferior ST segment elevation (2 3 and aV_F) was present in a few cases of right coronary artery spasm but was relatively more common with circumflex coronary artery spasm This finding did not really help to differentiate between the two vessels

ST segment elevation in Lead V_1 along wit

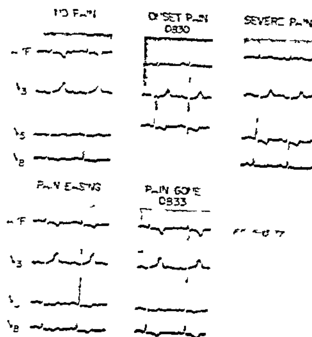


Fig 2 Selected ECG leads recorded during coronary arteriography of the same patient whose angiograms are shown in Fig. 1. During the height of her anginal attack, *immediately* prior to the arteriogram shown in *Fig 1C* the following changes were noted previously depressed ST has become isoelectric and previously inverted T has become upright in Lead aV previously elevated ST in Lead V has become slightly depressed previously isoelectric ST has become depressed with new T inversion in Lead V *T U fusion* is present in Lead V. These are the maximum ST and T wave changes seen during any of her anginal attacks. After subsidence of the attack, the ECG reverted to its preanginal configuration.

inferior ST elevation was present in two cases with right coronary artery spasm and was not seen with circumflex coronary artery spasm

In one case spasm in the circumflex coronary artery was limited to a large marginal branch and ST segment elevation was limited to Leads V and V

ST segment elevation in Leads 1 aV_R aV_L V, V or V was not observed with spasm limited to the right coronary artery or to the circumflex coronary artery (although the number of observations involving the latter artery is admittedly small)

With severe spastic obstruction of the anterior descending coronary artery, ST segment elevation was almost always seen in Lead V and V. One exception was reported where ST elevation was limited to Lead 1 aV and V to V. Although with spasm of this vessel ST elevation was commonly also seen in Leads 1 aV_L V V V_5 or V_6 these leads were not as sensitive for detection as were V_2 or V_3. Moreover Leads V, V and V_6 lacked specificity for anterior descending spasm

ST segment elevation in Lead 2, 3 or aV_F as a result of anterior descending spasm was not observed in these patients but has been reported to occur in some patients with long extensions of the anterior descending artery around the apex into the inferior interventricular groove

ST segment depression (presumably reciprocal to posteroinferior ST elevation) was commonly but not invariably seen in Leads 1 aV_L V, V in cases of right or circumflex coronary artery spasm. Reciprocal ST depression, also seen in Leads V_5 and V_6 in some cases of right coronary arterial spasm was uncommon in these leads with circumflex coronary artery spasm

With anterior descending spasm if reciprocal ST segment depression was present, it was more likely to be seen in Leads 2, 3 or aV_F and rather in Leads V_5 or V_6

Acute severe obstruction of two major coronary arteries due to simultaneous spasm of both vessels was occasionally seen. In one of our cases and in a case reported by Endo and associates,[3] combined involvement of the right and circumflex coronary arteries produced ST elevation in Leads 1 2, 3 aV_F and V, and V. The presence of ST elevation in Lead 1 has never been observed with isolated right coronary artery spasm so that these changes are quite suggestive of simultaneous involvement of the circumflex artery or of a dominant circumflex artery alone. Although one might assume that the absence of ST elevation in Leads V to V_4 mitigates against simultaneous involvement of the anterior descending artery this in fact cannot be relied on: a case reported by Berman and co-workers simultaneous spasm of the anterior descending (distal to a major diagonal branch) and circumflex arteries was associated with ST elevation limited to Leads 1 2 3 aV_F and V_6

Combined spasm of anterior descending and circumflex arteries in one other instance produced ST elevation in Leads 2, 3 aV_F V_1 to V; in another case it caused ST elevation in 2, 3 aV, V, to V and in yet another case it was associated with ST elevation limited to Lead 1 V_5

Lead showing greatest ST segment shift

Table II Lead distribution of greatest ST segment shift in patients with variant angina

	Inferior or infero lateral ST elevation (n = 67)			Anterior or antero-lateral ST elevations (n = 39)		
	% of cases showing	% of cases showing	% of cases showing	% of cases showing	% of cases showing	% of cases showing
ECG lead	Greatest ST elevation in this lead	Greatest ST depression in this lead*	No ST shift in this lead†	Greatest ST elevation in this lead	Greatest ST depression in this lead	No ST shift in this lead†
1	0	1	27	3	2	40
2	14	0	0	0	17	26
3	51	0	0	0	44	28
aV	0	1	75	0	5	79
aV	0	44	4	3	0	36
aV	30	0	0	0	19	26
V	2	0	37	0	0	28
V	0	29	28	23	0	1
V	1	14	30	46	0	1
V	0	6	39	24	2	1
V	0	1	40	0	2	32
V	2	3	42	0	9	36

In cases where the greatest ST shift was equal in 2 o 3 leads, ½ o ⅓ credit was given to each lead respectively for that case Total may not add up to exactly 100% because of rounding off to n arest whole number

†Total adds up to more than 100% because more than one lead per case usually had n ST segment shift

Infer ST elevation means ST levat n in Leads 3 and aV Inferolate al ST elevation means ST elevation in Leads 2 3 aV and in V or V as well Antero ST ele ation m ans ST elev tion in Leads V –V anterolateral ST el vation means ST el vation in Leads V_1–V and concomitantly also in Leads V and V and/ 1 and aV_L

Table II shows the relative frequency with which the greatest amount of ST segment elevation was demonstrated in the 12 leads of the standard ECG during variant angina attacks in the 114 cases of group B

With inferior or inferolateral ST segment elevation the degree of ST shift in Leads 2 3 and aV_F in a given case was usually nearly equal But where differences existed the greatest amount of ST elevation was usually present in Lead 3 and the least was present in Lead 2 There were rare cases where the maximum ST segment elevation was seen in Lead V (two cases) or in V (two cases)

With anterior or anterolateral ST segment elevation the greatest ST segment shift was usually seen in Lead V_3 less frequently in Leads V or V and rarely in Lead 1 or aV_L

Maximal reciprocal ST segment depression in cases of inferior or inferolateral ST elevation was most frequently seen in Lead aV_L less commonly seen in Leads V to V and rarely seen in Lead 1 aV_R V or V With anterior or anterolateral ST segment elevation greatest reciprocal ST depression was usually seen in Lead 3 less commonly seen in Leads 2 aV_F or V_6 and rarely seen in Leads 1 aV_R or V_5 The lead least likely to show any ST segment shift with either inferior or anterior ST elevation was aV_R

Discussion

Critique of methods Not insisting on recording of the multilead ECG demonstrating ST segment elevation *simultaneously* with the angiographically demonstrated coronary arterial spasm producing the variant angina attack allows criticism of this study on the ground that the location of spasm could move from one vessel to another from one attack to another and the vessel in spasm during the ECG recording might be different from the vessel seen to be in spasm at angiography This type of criticism is also applicable to my inclusion of cases of coronary spasm induced by drugs Anyone having experience with large numbers of these patients knows how difficult it is to obtain a multilead ECG during an attack and how much more difficult it is to obtain a coronary arteriogram during an attack. One would think that it would be easy to obtain a multilead ECG lead during the presence of coro

nary spasm during arteriography In actual practice most angiographic laboratories are (unfortunately) set up to monitor only one ECG lead during arteriography The attacks of spasm are evanescent and the gross changes in the ECG produced by selective coronary injection of contrast medium markedly reduce the time available to record the ECG alterations due to the spasm itself[80] All this has conspired to produce a situation where actual multilead ECG recordings of variant angina attacks during coronary arterial spasm simultaneously documented angiographically are rare indeed

Thus in order to obtain the relatively large number of observations to address the question in this study, compromises on that which is ideal have been made That these compromises are reasonable is indicated by the fact that in my experience and that of others repeated attacks of variant angina usually involve the same coronary artery in a given patient Although exceptions occur they are relatively rare the reported incidence being between 5% and 15% of all variant angina cases[1,91,93] Likewise variant angina attacks provoked the ergonovine maleate almost always involve the same coronary artery distribution as the spontaneous attacks[1,16,7,87]

This study does not deal with the problem of ST segment *depression* resulting from subendocardial ischemia produced by coronary artery spasm resulting in a lesser degree of obstruction than that required to cause ST segment elevation There is probably no qualitative difference between the spasm causing ST depression and that causing ST elevation and both can occur in the same leads in the same patient during different phases of one attack of variant angina or during different attacks[1]

ST elevation and coronary spasm correlation It is of course not surprising that anterior descending coronary arterial spasm produces ST elevation in the anterior precordial leads and that right coronary artery spasm produces ST elevation in Leads 2 3 and aV_F This is consistent with the results of ECG arteriographic correlations in patients with old transmural myocardial infarction[8] The *insensitivity* of Leads V and V_6 in showing ST elevation with acute anterior descending obstruction is not so well known however These latter leads are also very *nonspecific* for localizing the coronary artery involved since they may show ST elevation with obstruction of any of the three major coronary arteries Also it is [not] generally appreciated that Lead V_1 can show ST elevation in some cases of right coronary artery obstruction presumably due to anterior right ventricular ischemia Also Lead V_1 is relatively insensitive in detection of ST shift due to anterior descending obstruction

This is of clinical importance because even at present leads equivalent to V_1 are commonly used as the single monitored lead for detecting rhythm disorders in the coronary care unit (CCU) or with Holter type monitoring and leads equivalent to V_5 or V_6 are similarly used as single leads to search for ischemic ST segment shift in CCU with Holter type monitoring and during exercise testing These practices will result in missing many cases of transient ST elevation Even if it is caught ST elevation in these leads gives relatively little information about the coronary artery involved If ST depression reciprocal to ST elevation elsewhere were seen in these leads and interpreted as indicating subendocardial ischemia the clinician would be misled about the location of the ischemic myocardium and perhaps even about the nature of the ischemic attacks

It is also not widely appreciated that ST segment elevation in Leads 2 3 and aV_F does not unequivocally distinguish between obstruction of the right coronary artery and that of the circumflex coronary artery even in cases of right coronary artery dominance The electrocardiogram during an attack does not allow such a distinction to be made unless there are additional findings such as ST elevation in Lead V_1 (not seen in circumflex obstruction) or transient supra-Hisian AV block when the source of the artery to the AV node is known Spasm of the circumflex artery is thus one possible explanation for the failure to see obstruction develop in the right coronary artery during variant angina associated with inferior ST segment elevation[2,88] Undoubtedly the great variability of the amount of posteroinferior left ventricle supplied by the right and circumflex coronary arteries (with complete left coronary dominance at one extreme and marked right coronary dominance at the other) accounts for the ambiguity of ST elevation in Leads 2 3 and aV_F[88]

The presence of ST elevation simultaneously in Leads 2 3 and aV_F and anterior precordial leads V to V_4 suggests spasm involving two arteries

interior descending with either circumflex or ght coronary artery) or possibly the left main oronary artery Also ST elevation in Lead 1 long with that in Leads 2 3 and aV_F indicates involvement of at least some part of the left oronary artery system[97]

Even a full standard 12 lead ECG will fail to how any ischemic ST segment shifts on occasion uring complete spastic occlusion of a major oronary artery In some cases this may be ecause there was no ischemia produced[9, 99] due o an alternate source of blood to that distribu ion such as from a collateral circulation not etected at angiography or perfusion of the distal ed by a bypass graft[100] In other cases angina ould be produced and ischemia be present in an rea of the left ventricle not well covered by the tandard ECG (specifically high posterior left entricular wall ischemia due to obstruction of he circumflex artery[7])

Selection of leads to monitor It can be seen rom the foregoing that no single ECG lead will uffice to detect all possible episodes of ST seg nent elevation due to coronary artery spasm The more leads that are used the more sensitive will be the detection system But there are prac ical constraints In many places there is facility or only single lead monitoring

For detecting ST elevation due to spastic obstruction of the anterior descending coronary artery Lead V_3 combines the advantages of greatest sensitivity specificity and degree of ST segment change Lead V runs a close second For detecting inferior ST segment elevation due to spastic obstruction of either the right coronary artery or circumflex coronary artery Leads 3 and aV_F are almost equally good with Lead 3 having a slight advantage in showing a greater magnitude of ST shift

Of 339 cases of variant angina gathered from my own series and from the world literature in whom Leads 3 and V_3 were recorded during an attack having ST elevation in some lead the ST elevation was documented in either Lead 3 or V_3 (or rarely both) in 333 cases (98 2%) Of the remaining six cases primarily involving localized lateral ST elevation the ST elevation would have been detected in five by the addition of Lead aV_L and in three by the addition of Lead V or V_6 or by addition of Lead 1

Thus if one can monitor only one lead and there is no clue as to where the ST elevation will appear (such as T wave inversions between attacks or known single vessel coronary stenosis) then Lead 3 is a reasonable choice since inferior ST elevation is slightly more common in variant angina than anterior ST elevation If two leads can be monitored Leads 3 and V_3 will assure an excellent chance of detecting any ST elevation If three leads can be observed simultaneously lead aV_L could be added although I prefer to use V_5 or V instead for exercise or pacing tests since what sensitivity is lost in picking up ST elevation is more than made up for by the increased sensitiv ity of these latter leads in detecting ischemic ST segment depression of subendocardial ischemia

Summary

The lead distribution of ST segment elevation produced by severe spasm of major coronary arteries was correlated with the specific artery involved in a group of 110 cases of variant angina with single vessel coronary arterial spasm made up from eight cases personally observed and 102 cases abstracted from published literature

The most sensitive and specific lead for ST elevation during anterior descending (LAD) coro nary arterial spasm was V_3 V was almost as good For spasm of either the right (RCA) or circumflex coronary artery (CMFX) Leads 3 and aV_F showed ST elevation most frequently elec trocardiographically it was difficult to distinguish between spasm of these two vessels ST elevation in Leads V and V_6 was not specific occurring in some cases of spasm of each of the three major coronary arteries ST elevation in Lead V_1 occurred in either RCA or LAD spasm but never in CMFX spasm ST elevation in Lead 1 was never seen with isolated RCA spasm

No single lead can detect all cases of transient ST elevation Simultaneous monitoring of Leads 3 and V_3 would have detected 98 2% of 333 cases of ST elevation reviewed and addition of Lead aV_L would have detected most of the remainder These findings should be considered in lead selec tion for monitoring to detect ST elevation and in using the ECG to identify spastic coronary arte ries

I am very grateful to Mrs. Jeanne Yamaguchi for her kind and patient assistance in preparing this manuscript.

REFERENCES

1 Maseri A., Severi, S., DeNes M L Abbate A., Chier chia S Marzilla M., Ballestra A. M Parodi, O

Biagini A and Distante A Variant angina one aspect of a continuous spectrum of vasospastic myocardial ischemia Am J Cardiol 42 1019 1978
2 Wiener L Kasparian H Duca P R Walinsky P Gottlieb R S Hanckel F and Brest A N Spectrum of coronary arterial spasm Clinical angiographic and myocardial metabolic experience in 29 cases Am J Cardiol 38 945 1976
3 Distante A Severi, S Biagini, A and Maseri A Clinical results with nitrates in patients with primary angina at rest in Maseri A Klassen G A Lesch M eds Primary and Secondary Angina Pectoris New York 1978 Grune & Stratton Inc pp 389 395
4 Curry R C Pepine C J Sabom M B Feldman R L Christie L G Varnell J H and Conti C R Hemodynamic and myocardial metabolic effects of ergonovine in patients with chest pain Circulation 58 648 1978
5 Yasue H Touyama M Kato H, Tanaka S and Akiyama F Prinzmetal s variant form of angina as a manifestation of alpha adrenergic receptor mediated coronary artery spasm documentation by coronary arteriography AM HEART J 91 148 1976
6 Widlansky S McHenry P L Corya B C and Phillips J F Coronary angiographic echocardiographic and electrocardiographic studies on a patient with variant angina due to coronary artery spasm AM HEART J 90 631 1975
7 Heupler F A Proudfit W L Razavi M Shirey E K Greenstreet R and Sheldon W C Ergonovine maleate provocative test for coronary artery spasm Am J Cardiol 41 631 1978
8 Schroeder J S Bolen J L Quint R A Clark D A Hayden W G Higgins C B and Wexler L Provocation of coronary spasm with ergonovine maleate New test with results in 57 patients undergoing coronary arteriography Am J Cardiol 40 487 1977
9 Wiener L Kasparian H., Duca P R Walinsky P Gottlieb R S Hanckel F and Brest A N Spectrum of coronary arterial spasm Clinical angiographic and myocardial metabolic experience in 29 cases, Am J Card ol 38 945 1976
10 Higgins, C B Wexler L Silverman J F and Schroeder J S Clinical and arteriographic features of Prinzmetal s variant angina documentation of etiologic factors Am J Cardiol 37 831 1976
11 Dhurandhar R W Watt D L Silver M D Trimble A S and Adelman A C Prinzmetal s variant form of angina with arteriographic evidence of coronary arterial spasm Am J Cardiol 30 902 1972
12 Prchkov V K Mookherjee S Schiess W and Obeid A I Variant anginal syndrome coronary artery spasm and ventricular fibrillation in absence of chest pain Ann Intern Med 81 858 1974
13 Kerin N and Macleod C A Coronary artery spasm associated with variant angina pectoris Br Heart J 36 224 1974
14 Johnson A D Stroud H A Vieweg W V R and Ross, J Variant angina pectoris Clinical presentations coronary angiographic patterns and the results of medical and surgical management in 42 consecutive patients Chest 73 786 1978
15 Maseri A., Mimmo R Chierchia S Marchesi C Pesola A. and L Abbate A Coronary artery spasm as a cause of acute myocardial ischemia in man Chest 68 625 1975
16 Bramucci E., Specchia G deServi S Anoli L. Mussini, A., Marinoni, G P Cavazzi A Falcone C Valsecchi, O., and Montmartini C Reproducibilita del quadro clinico elettrocardiografico e coronarografico dello spasmo coronarica spontaneo mediante ergonovina ...
G Ital Cardiol 8 489 1978
17 Schroeder J S Silverman J F and Harrison, D ... Right coronary artery spasm causing Prinzmetal's ... ant angina Chest 65 573 1974
18 Yasue H Nagao M Omote S Takizawa A, M... and Tanaka S Coronary arterial spasm and Prinzmetal s variant form of angina induced by hyperven... and Tris buffer infusion Circulation 58 56, 19...
19 Ricci D R Orlick A E Doherty P W Cipriano ... R and Harrison D C Reduction of coronary b... flow during coronary artery spasm occurring spontaneously and after provocation by ergonovine ... Circulation 57 392 1978
20 Curry R C Pepine C J Sabom M B Feldman, R ... Christie L G and Conti C R Effects of ergonovine ... patients with and without coronary artery disease Circulation 56 803 1977
21 Kleinfeld M J and Rozanski J J Alternans of the ... segment in Prinzmetal s angina Circulation 55 ... 1977
22 Cheng T O Bashour T Kelser G A Weiss L ... Bacos J Variant angina of Prinzmetal with ... coronary arteriograms A variant of the variant Circulation 47 476 1973
23 Endo M Hirosawa K Kaneko N Hase K In... and Konno S Prinzmetal s variant angina Coronary arteriogram and left ventriculogram during ... attack induced by methacholine N Engl J M... 294 252 1976
24 Oliva P B Potts D E and Pluss P G Coronary arterial spasm in Prinzmetal angina Documentation ... coronary arteriography N Engl J Med 288 ... 1973
25 Groves B M Variant angina an electrocardiographic and arteriographic spectrum produced by coronary artery spasm Curr Probl Cardiol 2(4) 1 19...
26 Higgins C B Wexler L Silverman J F Hayden ... G Anderson W L and Schroeder JH Spontaneous and pharmacologically provoked coronary arterial ... in Prinzmetal variant angina Radiology 119 ...
27 Hart N J Silverman M E and King S B ... angina pectoris caused by coronary artery spasm ... Med 56 269 1974
28 Berman N D McLaughlin P R Huckell V ... Mahon W A Morch J E and Adelman, A ... Prinzmetal s angina with coronary artery spasm ... graphic pharmacologic metabolic and radionuclide ... fusion studies Am J Med 60 72... 1976
29 Curry R C Jr Prinzmetal s angina Provocat... and current therapy J.A.M.A 240 677 1974
30 Bertrand M E Laisne C Lefebvre J M Carré ... Warembourg H Jr., and Lekieffre J Le spasme ... artères coronaires Arch Mal Coeur 70 1233, 19...
31 Froment R Normand J and Amiel L A ... poitrine du type Prinzmetal Coronaires ... mais spasme de l inter ventriculaire antérieure en ... de crise Arch. Mal Coeur 66 765 1973
32 Cipriano I R Guthaner D F Orlick A F Ric... R Wexler L and Silverman J F The ... ergonovine maleate on coronary arterial size Circulation 59 82 1979
33 Hiltgen M Guermonprez J L Sellier P Gerbaux ... and Maurice P Angor de Prinzmetal A propos ... cinéangiographies coronaires sélectives et de ... tions (pontages aorto-coronaires) Arch Mal C... 66 553 1973
34 Rizzon P., Rossi L Calabrese P Franchini G ... DiBiase M Angiographic and pathologic correla...

Prinzmetal variant angina Angiology 29 486 1978

King M J, Zir L M Kaltman A J and Fox A C Variant angina associated with angiographically demonstrated coronary artery spasm and REM sleep Am J Med Sci 265 419 1973

Hansen J F and Sande E Treatment of Prinzmetal s angina due to coronary artery spasm using verapamil a report of three cases, Europ J Cardiol 7 327 1978

Mathey D Montz R Hanrath P Knop J Kupper W Schneider C and Bleifeld W Kurzfristige regionale Myokardischamie und ihre Folgen bei Prinzmetal—Angina pectoris Dtsch Med Wschr 103 969 1978

Chahine R A and Raizner A E Another look at Prinzmetal s variant angina Europ J Cardiol 6 71 1977

Angoli L Marinoni, G P Falcone C Bramucci, E DeServi, S Specchia G and Montemartini C Spasme coronarien à l effort Demonstration coronarographique d un cas Arch Mal Coeur 71 823 1978

Marsh, C A Benchimol A and Desser K B Variant angina pectoris Pain and arrhythmias controlled after postoperative myocardial infarction J A.M.A 235 833 1976

Taurino L Storelli A and Roma F I farmaci Ca antagonisti nell angina di Prinzmetal Boll Soc Ital Cardiol 21 1111 1976

Specchia G DeServi S Falcone C Bramucci, E Angoli, L Mussini A Marinoni, G P Montemartini C and Bobba P Coronary arterial spasm as a cause of exercise induced ST-segment elevation in patients with variant angina Circulation 59 948 1979

Levine S Intestinal infarction without vascular occlusion Am J Proctol 10 257 1959

Nordstrom, L A Lillehei J P Adicoff A Sako Y and Gobel F L Coronary artery surgery for recurrent ventricular arrhythmias in patients with variant angina, Am Heart J 89 236 1975

Betriu A Solignac, A and Bourassa M G The variant form of angina diagnostic and therapeutic implications Am Heart J 87 272 1974

Nelson C Nowak, B Childs H, Weinrauch L and Forwand S Provocative testing for coronary arterial spasm rationale risks and clinical illustrations Am J Cardiol 40 624 1977

Bharati S Dhingra R C Lev M Towne W D Rahimtoola S H and Rosen K M Conduction system in a patient with Prinzmetal s angina and transient atrioventricular block, Am J Cardiol 39 120 1977

McLaughlin P R Doherty P W, Martin R P, Goris M L and Harrison D C Myocardial imaging in a patient with reproducible variant angina Am J Cardiol 39 126 1977

Guazzi, M Olivari, M T Polese A, Fiorentini C and Magrini, F Repetitive myocardial ischemia of Prinzmetal type without angina pectoris Am J Cardiol 37 923 1976

Shubrooks S J Bete J M Hutter A M, Block, P C Buckley M J Daggett W M and Mundth E D Variant angina pectoris clinical and anatomic spectrum and results of coronary bypass surgery Am J Cardiol 36 142 1975

Williams R R Wagner G S and Peter R H ST-segment alternans in Prinzmetal s angina, Ann Intern Med 81 51 1974

Gorfinkel H J Inglesby T V Lansing A M and Goodin R R ST segment elevation transient left posterior hemiblock and recurrent ventricular arrhythmias unassociated with pain A variant of Prinzmetal s anginal syndrome Ann Intern Med 79 795 1973

53 Athanassopoulos C B and Maroutsos C G Prinzmetal s angina Br Heart J 39 911 1977

54 Weiner D A Schick, E C, Hood W B, and Ryan T J ST-segment elevation during recovery from exercise A new manifestation of Prinzmetal s variant angina, Chest 74 133 1978

55 Gaasch, W H, Lufschanowski, R Leachman R D and Alexander J K Surgical management of Prinzmetal s variant angina Chest 66 614 1974

56 Muller J E and Gunther S J Nifedipine therapy for Prinzmetal s angina Circulation 57 137 1978

57 Fortuin N J and Friesinger G C Exercise-induced ST segment elevation Clinical electrocardiographic and arteriographic studies in twelve patients, Am J Med 49 459 1970

58 Bobba P, Vecchio C, DiGuglielmo L Salerno J Casari, A and Montemartini, C Exercise-induced RS-T elevation Electrocardiographic and angiographic observations, Cardiology 57 162 1972

59 ECG of the Month, J Tennessee Med Assoc 66 128 1973

60 Bentivoglio L G Ablaza, G G and Greenberg L F Bypass surgery for Prinzmetal angina Arch Intern Med 134 313 1974

61 Gianelly R, Mugler F, and Harrison D C Prinzmetal s variant of angina pectoris with only slight coronary atherosclerosis, California Med 108 129 1968

62 Bobba P, DiGuglielmo L Vecchio C and Montemartini, C Coronarographic patterns in Prinzmetal s variant angina Acta Cardiol 26 568 1971

63 Renggli, I and Burkart F Prinzmetal Angina Klinik und koronarographischer Befund Schweiz Med Wschr 106 141 1946

64 Dupasquier E Bugnon A Fellay G Grbic M Braaker P and Monney A Angor de Prinzmetal A propos de 4 observations Revue de la littérature Schweiz Med Wschr 105 1246 1975

65 Cherrier F, Cuilliere M Dodinot, B and Hua G Angor de Prinzmetal aspects coronarographiques considerations therapeutiques A propos de 7 observations, Arch Mal Coeur 66 579 1973

66 Christian N and Botti, R E Prinzmetal s variant angina pectoris with prolonged electrocardiographic changes in the absence of obstructive coronary disease Am J Med Sci 263 225 197

67 Pretolani, E and Zoli, I Su un caso di variant angina" di Prinzmetal esito a distanza di un intervento di doppio Cardiol Prat 24 297 1973

68 Bobba P, Vecchio C, DiGuglielmo L, Montemartini C Salerno J A and Casari A Modificazioni ecgrafiche transitorie tipo variant angina di Prinzmetal indotte da prova da sforzo Cardiol Prat 22 337 1971

69 Buonanno C Arteriografia coronarica negativa in pazienti con sindrome anginosa ed anomalie electrocardiografiche Giorn Ital Cardiol 1 340 1971

70 Kleiber G E Schatz I J Kirsh M M, and Sodeman T M Variant angina clinical laboratory and operative study of eight cases J Am Osteop Ass 76 880 1977

71 Finardi, G Venco A, and Fogari R Rilievi cinetocardiografici in un caso di angina di Prinzmetal studiato anche coronarograficamente Giorn Ital Cardiol 1 244 1971

72 Buonanno C Mancuso M Zanini, S, Besa G and Poppi, A Diagnosi e trattamento dell insufficienza coronarica acuta Giorn Ital Cardiol 2 893 1972

73 Bertini, G Cucurnia M G Fumagalli C Marchionni N Pini, R and Vannucci, A Angina di Prinzmetal Descrizione anatomoclinica di un caso con circolo

coronarico indenne Minerva Cardioangiol 26 15 1978

74 Riesco C D Domenech Delgado J., Poveda Sierra J J Prieto Solis J A., and Pajaron Lopez A Angor de Prinzmetal Caracteristicas poco habituales Rev Clin Esp 143 175 1976

75 Courtadon M., Jourde M., Alix, B Brivady A., Vial let J F., and Jallut H Modifations électrocardiographiques de type Prinzmetal" provoquees par epreuve d effort A propos de 2 cas Coeur 4 729 1973

76 Masson J F., Guermonprez J L and Maurice P Sus-decalage du segment ST à l electrocardiogramme d effort Corrélation avec la coronarographie Arch. Mal. Coeur 68 729 1975

77 Treir G P., Thiene G., Benussi, P., Marini, A Caobelli, A., Frasson F., Ambrosio G B., and Dal Palu C Prinzmetal s variant angina Clinical angiographic and pathological correlations in two typical cases Europ J Cardiol. 4 319 1976

78 Marcus H R., and Easley R M Jr The effectiveness of high dose beta blockade in patients with variant angina pectoris Rhode Isl. Med J 61 159 1978

79 Norro G H. A. C., and Roos J P Prinzmetal s variant angina Acta Cardiol 31 491 1976

80 Malcolm I D., Sniderman A., and Morin J E Successful coronary artery bypass surgery in an 80-year-old man with Prinzmetal s angina Can. Med Assoc. J 119 749 1978

81 Arrigo F., Coglitore S Virga T., Giannetto M Bramanti, O., Melluso C., and Consolo F Angina di Prinzmetal. Considerazioni a proposito di un caso clinico Boll. Soc Ital. Cardiol. 22 283 1977

82 Curry C L., and Andy J J Variant angina pectoris Four cases to illustrate the spectrum J Natl. Med Assoc 67 349 1975

83 Swider L., and Šafarils, J Prinzmetalova angina pectoris bez koronarografického prukazu změn benčitych tepen Vnitr Lek 24 372 1978

84 Vazquez García F M., Errazquin Saenz de Tejada, F Burgos Cornejo J., Corredor Morales A., Fournier Andray J A. Moron del Valle J M., Duran Freire E Pineda Sánchez A., and Pedrote Guinea J A. Angina de pecho invertida estudio de siete casos, Rev Esp Cardiol. 27 19 1974

85 Levene D L., and Freeman M R α adrenoreceptor mediated coronary artery spasm, J.A.M.A 236 1018 1976

86 Straub E J Pupello D F., and Harrison E E Onset of Prinzmetal s angina two years following sudden death syndrome survival JACEP 6 405 1977

87 Curry R C., Jr Pepine C J Sabom M B., and Conti, C R. Similarities of ergonovine induced and spontaneous attacks of variant angina Circulation 59 307 1979

88 Curry R. C Ergonovine and variant angina Circulation 60 217 1979

89 Maseri A., Severi, S., DeNes, M L Abbate A., Chierchia S., Marzilli, M Ballestra, A. M., Parodi, O Biagini, A., and Distante A. Variant angina: one aspect of a continuous spectrum of vasospastic myocardial ischemia Am J Cardiol 42 1019 1978

90 MacAlpin R N., Weidner W Kattus, A. A., and Hanafee W Electrocardiographic changes during selective coronary angiography Circulation 34 [illegible] 1966

91 Maseri, A., Severi, S Chierchia, S Parodi, O and Biagini, A Characteristics, incidence and pathogenetic mechanism of "primary" angina at rest, in Maseri A, Klassen G A., and Lesch M eds., Primary and Secondary Angina Pectoris New York, 1978 Grune & Stratton, Inc., pp 265-273

92 Hosoda S., and Kimura, E Efficacy of nifedipine in variant form of angina pectoris in Jatene A. D and Lichtlen P R., eds. 3rd International Adalat Symposium New Therapy of Ischemic Heart Disease International Congress Series No 388, Amsterdam, 1976 Excerpta Medica pp 195-206

93 Benacerraf A., Brau J Castaigne A Ducimetière P Farah E., Furman P., Lellouche D Rosenstein E Starckman G., and Tonnelier M., Angor de Prinzmetal. A propos de 55 observations, Coeur 9 [illegible] 197[illegible]

94 Williams R A Cohn P F., Vokonas, P S., Young E Herman, M V., and Gorlin R. Electrocardiographic, arteriographic and ventriculographic correlations in transmural myocardial infarction Am. J Cardiol 31 595 1973

95 Gaasch, W H., Adyanthaya A. V Wang, V E. Pickering E., Quinones M A and Alexander J K Prinzmetal s variant angina hemodynamic and angiographic observations during pain Am. J Cardiol 35 683 1975

96 MacAlpin R N., Abbasi, A S Grollman, J and Eber L. Coronary artery size during life a cinearteriographic study Radiology 108 567 19 3

97 Leclercq J F Lavalle J P Masquet C H and Bouvrain, Y Correlation between angiographic and ECG signs location in unstable angina Europ J Cardiol. 9 181 1979

98 Rose F J Johnson A D., and Carleton, P A. S[illegible] of the left anterior descending artery Chest 65 [illegible] 1974

99 Guermonprez J L. Guéret P Camilleri, J P Carpentier J., Deloche A and Maurice P Angor de Prinzmetal. Etude histologique coronarie de prélèvements peropératoires. A propos de deux cas, Arch. Mal Coeur 70 301 1977

100 Pachinger O M and Judkins M P Coronary bypass surgery in Prinzmetal angina, Europ J Cardiol 2 [illegible] 1975

Prognostic significance of an ST segment depression of patients with an acute coronary attack

H Raunio
V Rissanen
O Rehnberg
Y Jokinen
M Helin
K Pyorala
Kuopio Finland

An ST segment elevation as an indicator of myo cardial injury is well known Several studies based on the 12 lead ECG or on surface mapping deal with this ECG pattern On the other hand the opposite pattern an ST segment depression has stirred little interest among researchers excluding studies on exercise stress ECG

A depressed ST segment has traditionally been connected with a subendocardial myocardial infarction (MI) or regarded as a reciprocal sign of an ST segment elevation in the opposite leads[3] In an earlier autopsy study we showed that an ST segment depression of a definite shape and depth in an ECG taken shortly before death was found in 88% of patients with an acute circumfer ential subendocardial MI and in 43% of those with a regional subendocardial MI or a transmu ral MI An ECG taken at admission may even indicate the prognosis of a patient with an acute MI ST segment depression was found in half of the patients who died within three weeks[4]

The shape of the ST segment depression as well as its depth are usually well defined in studies on exercise stress ECG but we have found only a few studies dealing with the conventional ECG that give exact definitions of the shape of the segment and of the depth of the depres sion[5-7] Since a specific type fo the ST segment depression seems to occur frequently in patients with various types of acute MIs leading to death further studies on this ECG pattern in patients with an acute attack of chest pain seem neces sary

Material and methods

The original series consisted of 636 patients (424 men and 212 women) admitted to the Kuopio University Central Hospital during a period of 14 months because of an acute attack of chest pain lasting at least 20 minutes Patients whose attack was considered of extracardiac origin were not included in the series nor were patients who died before the first day ECG recording (14 patients) nor were those with a right or left bundle branch block or a ventricular rhythm including patients with artificial pacemakers The material of this analysis was thus composed of a total of 580 patients 386 men and 194 women The age of the men ranged from 28 to 89 years with a mean of 59 years and of the women from 37 to 86 years with a mean of 65 years

Electrocardiography The ECGs were recorded with an ink jet recorder with a frequency response of 0 to 700 cycles per second (Olli 326 Kone Instruments Helsinki Finland)

The electrocardiograms were analyzed by an experienced reader The ECGs included in the study were recorded at the following phases in

From the Department of Medicine University of Kuopio Kuopio Finland

Received for publication Sept 6 1979
Accepted for publication Nov 9 1979

Reprint requests Dr H Raunio Department of Medicine University of Kuopio 70210 Kuopio 21 Finland

0002-8703/80/050565 + 09$00.90/0 © 1980 The C V Mosby Co

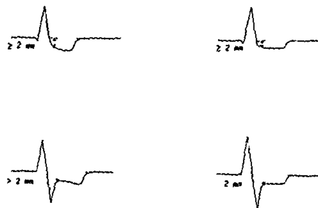


Fig 1 Various manifestations of definite ST segment depression The interval between the arrows is 2 mm (0 2 mV) or more

the morning of the first and the third day after admission at the end of the hospitalization period 6 weeks 3 6 and 12 months after admission

ST segment depression The J point depression was measured in millimetres with the P Q segment as the reference line Only cases with the J point followed by a horizontal or a downward sloping ST segment lasting at least 0 08 sec were noted Thus cases with a so called junctional ST segment depression showing an upward going ST segment were not included The depression of the isoelectrical line caused by an atrial T wave was noted and its depressing effect on the J point was eliminated

The ST segment depression was regarded as *definite* if the J point was depressed 2 mm or more at least in one lead and if it was followed by the above mentioned shape of the ST segment (Fig 1)

The QRS criteria of an MI and those of an ST segment elevation in a myocardial injury are presented in our earlier paper Left ventricular hypertrophy (LVH) was considered to be present if the height of the R wave in Leads V or V_6 was 26 mm or more or in any of the Leads I, II III or aV_F 20 mm or more or in lead aV_L 12 mm or more or if the sum of the height of the R wave in Lead V_5 or V and the depth of the S wave in Lead V_1 was 35 mm or more

In this study the E C G leads were grouped as follows

Leads I aV_L V i e the lateral lead set
Leads II III aV_F i e the inferior lead set
Leads V_1 V_2 i e the anterior lead set
Leads V_3 V_4 V_5 i e the anterolateral lead set

Clinical data The heart rate was measured from the first day ECGs The occurrence of chest pain during the first days of hospitalization was recorded according to the study plan The criteria used for a cardiogenic shock were the following systolic blood pressure below 100 mm Hg urinary secretion below 40 ml /minute, vasoconstriction in the periphery and signs of confusion

Laboratory diagnostics In the serum enzyme diagnostics of an acute MI the upper normal limit used for serum aspartate aminotransferase (ASAT or GOT) was 40 U /L +37° C and for serum creatine phosphokinase (CK) 200 U / +37° C In addition the serum enzyme curve had to show typical abnormal changes before it was considered indicative of an acute MI The lower normal limit of serum potassium was set at 3 9 mmol /L

Chest x ray study The chest x rays were from supine patients in the mornings of the first three days of hospitalization The radiographs were analyzed by a cardiologist The classification of pulmonary congestion into four was performed according to the method of Turner and associates [8] The heart size was estimated by the C/T ratio where C is the sum of the maximum distances of the right and left border of the heart from the medial line and T the maximum width of the osseous chest at the level of the heart-diaphragmatic angle

Division of the patients into groups according to the diagnostic criteria The patients were divided into the following groups

Group A Patients with typical chest pain serum enzyme changes indicative of a recent or patients with autopsy evidence of an acute (263 men and 110 women)

Group B Patients with a typical chest attack but no significant changes in the enzyme levels (49 men and 50 women) cases QRS signs of an MI were present remaining cases either an ST segment elevation of injury or an ST segment depression of or more was found if the depression developed in the acute phase and disappeared after days

Group C Patients with a typical chest attack but no serum enzyme reactions indicative of an acute MI (74 men and 34 women) changes which did not fulfill the criteria of B were found in the ECGs of these patients

Follow up Follow up examinations of

Table I Prevalence of an ST segment depression in the ECGs taken during the first three days of hospitalization in the material of 386 men and 194 women admitted to hospital because of a heart attack

	Depression of J point in millimeters										
		Definite ST segment depression									
Lead sets	1 1.9	2 2 9	3-3.9	4-4.9	5-5 9	6 6 9	7 mm or more	Total number of cases	Per cent	Total number of cases	Per cent
Men											
I aV V	23	13	3	1				17	4 4	40	10 4
II III aV	7	6						6	1 6	13	3 4
V V	8	10	6	2	3	2	1	24	6 2	32	8 3
V V V	37	26	11	5	4	2	4	52	13 4	89	23 1
Any of the lead sets	47	40	11	6	5	3	4	69	17 9	116	30 1
Women											
I aV V	29	12	1		1			14	7.2	43	22.2
II III aV	17	3	2					5	2 6	22	11.3
V V	29	7	2					9	4 6	38	19 6
V V V	25	28	7	4	2			41	21 1	66	34 0
Any of the lead sets	32	29	10	6	1			46	23 7	78	40.2

patients were performed after 6 weeks 3 6 and 12 months after admission Two hundred seventy nine men and 139 women attended the last follow up examination

One hundred eighteen patients (81 men and 37 women) died during the follow up year The mortality rate in Group A was 27 3% in Group B it was 13 1% and in Group C it was 2 8% A coronary heart disease was considered to be the basic cause of death of all but four persons in Group A of all in Group B and of all but one in Group C The four patients in Group A had a severe respiratory infection and the patient in Group C had an acute cerebral hemorrhage

Results

Prevalence of an ST segment depression A J point depression of 1 mm or more followed by a horizontal or downward sloping ST segment in any of the four lead sets was found in 30% of the male and in 40% of the female patients admitted to hospital because of an acute coronary attack (Table 1) The depression was most frequent in the anterolateral lead set (Leads V_3 V and V_5 Table I) Fifty eight men (15%) and 91 women (91%) had a depressed ST segment in two or more of the lead sets

A definite ST segment depression (the J point depression 2 mm or more) was found in any of the lead sets in 69 men (17 9%) and 46 women (23 7%) (Table I) The age of these men ranged from 36 to 89 years with the mean of 63 years and of the women from 56 to 85 years with the mean of 69 years The age of the remaining 317 men without a definite ST segment depression ranged from 28 to 86 years (mean 58 years) and of the 148 women from 37 to 86 years (mean 64 years) The patients with a definite ST segment depression thus were older than patients without this pattern ($p < 0\ 01$)

Correlation between the definite ST segment depression and an acute MI In 63 out of the 69 men and in 36 out of the 46 women with a definite ST segment depression the serum enzyme curve indicated an acute MI (Table II) Five of the six men and three of the ten women without enzyme reactions had had an old MI

The definite ST segment depression was only infrequently found in leads with QRS signs of MI or in the leads opposite to the leads showing Q waves of infarction Most frequently the pattern was associated with QRS signs of an inferior MI and was most commonly seen in Leads V_3 V or V_5 There were 39 patients in whom no QRS signs of an MI but a definite ST segment depression was seen (Table III) In 28 of them (71%) serum

Table II Distribution of the patients with a definite ST segment depression into three groups according to the reliability of the MI diagnosis*

	Men			*Women*		
	Total number of patients	*Number of patients with a definite ST segment depression*	*Per cent*	*Total number of patients*	*Number of patients with a definite ST segment depression*	*Per cent*
Group A	263	63	24 0	110	36	[illegible]
Group B	49	2	4 1	50	8	[illegible]
Group C	74	4	5 4	34	[illegible]	[illegible]
Total	386	69	17 9	194	46	[illegible]

A detailed definition of the groups is given in the section Material and methods

Table III QRS signs of an MI in the 115 patients with a definite ST segment depression figures indicate the number of patients

Leads with a definite ST segment depression	*QRS signs of an MI in leads*				*No QRS signs of an MI (39 cases)*	*Total number of cases with definite ST segment depression (115 cases)*	
	I aVL V (17 cases)	*II III aVF (45 cases)*	*V V (4 cases)*	*V V V (10 cases)*		*No*	*%*
I aV_L V	–	6	–	1	1	8	70
II III aV	2	–	1	3	–	6	[illegible]
V V	1	4	–	–	2	7	61
V V V	14	3[illegible]	3	6	36	94	81 8

Table IV ST segment elevation in patients with a definite ST segment depression figures indicate the number of patients

Leads with a definite ST segment depression	*ST segment elevation in the given leads*				*No ST segment elevation (78 cases)*	*Total number of cases with a definite ST segment depression (115 cases)*	
	I aVL V (4 cases)	*II III aVF (25 cases)*	*V V (5 cases)*	*V V V (3 cases)*			
I aV V	–	4	1	–	3	8	[illegible]
II III aV	2	–	2	2	–	6	[illegible]
V V	–	4	–	–	3	7	[illegible]
V V V	2	17	2	1	72	94	[illegible]

enzyme reactions indicated acute MI In these cases the definite ST segment depression was also most frequently found in one or more of the Leads V, V and V, The ST segment was elevated in 37 out of the 115 patients with a definite ST segment depression (Table IV) The elevation was most frequent in the inferior lead set while the definite ST segment depression of these patients most commonly occurred in the anterolateral leads In 78 patients a definite ST segment depression but no ST elevation was evident (Table IV) Sixty five of them belonged to Group A

The definite ST segment depressions f[illegible] the recordings on the first three days after[illegible] peared In 12 patients the depression w[illegible] found in the ECG taken at the end [illegible] hospitalization period In the EGCs taken [illegible] follow up studies the definite ST-[illegible] depression was found in 16 patients who [illegible] the pattern in the first day ECGs It w[illegible] found in the ECG of nine patients in [illegible] first-day ECGs this pattern was not seen [illegible]

Clinical correlations of the definite ST segment depression The mean heart rate [illegible] with a definite ST segment depression [illegible]

Table V Differences in certain clinical data between patients with and those without a definite ST segment depression in the ECGs recorded during the first three days of hospitalization

	Patients with a definite ST segment depression (total 115)			Patients without a definite ST segment depression (total 465)			
	Data available	Number of patients	Per cent	Data available	Number of patients	Per cent	Statistical significance
ECG signs of left ventricular hypertrophy	115	49	42.6	465	116	24.9	$p < 0.005$
Pulmonary congestion of Grade 3 or 4 in the first three days x ray study	106	51	48.1	441	123	27.9	$p < 0.01$
C/T ratio 0.6 or more	103	36	35.0	385	85	22.1	$p < 0.05$
Low serum potassium level in the first day	94	19	20.2	280	56	20.0	p = n.s.
Severe chest pain during the first day	107	40	37.4	440	150	34.1	p = n.s.
Occurrence of cardiogenic shock during the first day	114	7	6.1	460	14	3.0	p n.s.
Use of digitalis before admission	115	68	59.1	457	190	41.6	$p < 0.05$
Use of digitalis at the time of the one year follow up study	68	61	89.7	366	218	59.6	$p < 0.05$

minute (SD 27.4) and of women 91/minute (SD 25.7) The mean heart rate of men without the pattern was 83/minute (SD 24.3) and of women 89/minute (SD 23.9)

Electrocardiographic LVH was significantly more common in the ECGs of patients with a definite ST segment depression than in ECGs of patients without the pattern (Table V) Furthermore pulmonary congestion Grade 3 or 4 and a C/T ratio of 0.6 or more in any of the first three day examinations were more frequent in patients with a definite ST segment depression than in those without this pattern (Table V) There was also a significant difference between these patients in the prevalence of digitalis treatment both before admission and one year after admission (Table V) On the other hand there was no significant difference in the low serum potassium levels in the occurrence of persisting chest pain during hospitalization or in the occurrence of cardiogenic shock

Mortality rate of patients with an ST segment depression Within one year the mortality rate was lowest (14.2%) in patients with a J point depression less than 1 mm or no depression (Table VI) Both in men and women the mortality rate grew gradually with an increasing J point depression (Table VI) The highest mortality rate was found in men with a J point depression of 3 mm or more (55%) The one year mortality rate of men with a definite ST segment depression was 48% and of women it was 30% The one year mortality rate was also high in cases where the definite ST segment depression occurred in two or more lead sets i.e 19 of 35 men (54%) and six of 20 women (30%) died

The difference in the mortality rate between patients with and without the definite ST segment depression developed during the first four weeks (Fig 2) There was a significant difference in the mortality rate between these two groups during the first three days as well as during the first four weeks After four weeks the increase of the mortality rate was the same in both groups (Fig 2)

Discussion

The ST segment depression as defined in this study is rather a common ECG sign of coronary patients with an acute attack of chest pain In our series the prevalence was 19.8% When this ECG pattern occurs it seems to be of important clinical and prognostic significance During the hospitalization period evidence of an acute myocardial infarction (AMI) was found in up to 86% of the patients with this pattern observed during the first three days succeeding admission The pattern was frequent (14%) also in cases of AMI without conventional ECG signs of myocardial involvement After the acute phase the patt

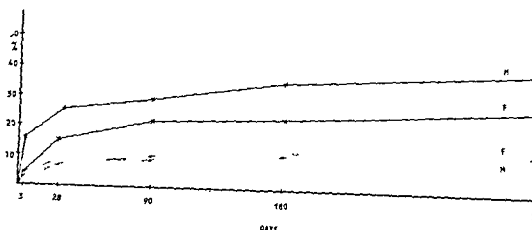


Fig 2 Cumulative graphs showing the mortality rates of patients with a definite ST segment depressi and of those without the pattern (-----) The exact time of death of four men and one woman with the patte of four men and two women without the pattern was not known

Table VI The mortality rate during the year after admission of the patients with varying d of a J point depression with a horizontal or downward sloping ST segment

	Men			*Women*			*Tot*	
	Number of patients	*Number of deaths*	*Per cent*	*Number of patients*	*Number of deaths*	*Per cent*	*Number of patients*	*Nu de*
Less than one mm or no ST depression	270	40	14 8	116	15	12.9	386	
One mm or more but less than 2 mm.	47	8	17 0	32	8	25 0	79	
Definite ST segment depression								
Two mm or more but less than 3 mm	40	17	42.5	29	8	27 6	69	2
Three mm or more but less than 4 mm.	11	6	54.5	10	5	50 0	21	1
Four mm or more	18	10	55 6	7	1	14 3	25	1
Total	386	81	21 0	194	37	19 1	580	11

tended to disappear being less frequent at the end of the hospitalization period After hospitalization the prevalence of the pattern was only slightly higher than that detected in population studies on middle aged Finnish people The high hospital mortality rate of patients with this ECG pattern naturally had a selective effect on the composition of the follow up material

Theories on the mechanism of the ST segment depression in AMI patients are rather controversial A pronounced shift of the J point in the ECG is regarded as an essential feature in patients with a myocardial injury Myers and colleagues demonstrated this already in 1951 Later experimental studies of Vincent and co workers have shown that a T Q segment (isoelect displacement due to the loss of resting potential is the major event resulti ST segment displacement (secondary cl cases of myocardial injury It is clear th cases the J point must be changed in proportion as the ST segment In th ECG this has been demonstrated in ST depressions if the injury is subendocard same type of ST segment depression w frequent finding particularly in the fi with circumferential subendocardial M earlier series [4] On the other hand action waveform changes (primary changes) responsible for changes in the ST segmen

however has a lesser role in cases of myocardial injury while in association with tachycardia and digitalis effect it is the major cause of ST segment changes[11, 12] In cases of tachycardia or digitalis treatment the primary waveform changes cause shortening of the ventricular action potential with a steep slope of repolarization in phase 2 [3] The latter part of the ST segment then is deformed and often leads to a strain type of ST segment depression In order to decrease difficulties in the interpretation and as its significance seems to be controversial we have not included the cases with the so called junctional ST segment depression (depressed J point followed by an upward going ST segment)

According to present understanding many transmural infarcts if not all are initially subendocardial and only secondarily become transmural Development of the myocardial injury to its total extent may last for hours or days A clearly necrotic center of an AMI particularly at the initial stage is surrounded by rather an extensive zone of severe ischemia liable to progress into injury This ischemic zone may be reflected as an ischemic ST segment depression in the ECG Progression of this critical zone into injury worsens the prognosis of the patient The high rate of mortality of AMI patients with an ST segment depression as well as the extensive acute myocardial lesions frequently revealed in fatal cases at autopsy suggest that the ischemic zone could be one explanation for the occurrence of this ECG pattern at the initial stage of an AMI The concept of an ischemic zone is also supported by our frequent findings of an ST segment depression in leads adjacent to leads with signs of an AMI The ST segment depression though possibly merely ischemic may if prolonged and if associated with significant changes in the enzymes represent subendocardial infarction circumferential or segmental but it may also relate to transmural infarctions Although the QRS signs of an MI were most frequently found in the inferior lead set in our patients we cannot connect a definite ST segment depression solely with an inferior wall myocardial infarction Possible changes associated with an anterior wall infarction may not have been detected because of the limited capacity of the 12 lead ECG to reflect the cardiac potential

Some researches emphasize the role of metabolic ionic or hemodynamic alterations as the basic cause of an ST segment depression[3, 13] This is supported by our unpublished results from an autopsy series of hospital deaths in which a definite ST segment depression was found in the ECG preceding death in some patients without coronary heart disease or a myocardial injury[14] LVH associated with myocardial fibrosis as well as an acute collapse due to various causes seem to be frequent findings in such cases

On the other hand there is certain evidence suggesting that an ST segment depression in an AMI is not caused by a myocardial injury Experimental studies have shown that an ST depression can originate from well perfused areas surrounding the injury[15, 6] Furthermore samples taken from myocardial segments producing an ST segment depression have shown that the CK enzyme is not released from such areas [6]

The ST segment depression in patients with an AMI can of course be reciprocal to the ST segment elevation of an injury However it is obvious that in the ischemic conditions there are ST segment depressions caused also by other mechanisms[13, 17, 8] This has also been proved experimentally

1 An ST segment depression frequently occurs near the periphery of an injured area[3, 17, 19]

2 An ST segment depression does not occur simultaneously with a maximum ST segment elevation[3, 23]

3 An ST segment depression is evanescent while an elevation tends to be more stable[3, 23]

4 In simultaneous recordings of the subendocardial and epicardial leads no relationship between the ST segment changes have been observed[3]

In this study the ECG signs of LVH as well as the use of digitalis were more frequent in patients with a definite ST segment depression than in those without the pattern Both LVH and digitalis therapy can of course make more pronounced the depth of the ST segment On the other hand treatment with digitalis and LVH in the ECG are indicators of a severe heart disease Enlargement of the heart and the frequent occurrence of pulmonary congestion in the early days of hospitalization in the x rays of patients with an ST-segment depression suggest a tendency to impaired functional performance of the heart Furthermore the higher age of these patients may simply be related to the advancement of heart diseases with age

Since the definite ST segment depression in an acute coronary attack seems to coincide with a severe degree of coronary heart disease, it is not surprising that during the one year follow up period the mortality rate of the patients with the depression in the acute phase was nearly three times as high as of the patients without the pattern The difference in the mortality rate developed during the first four weeks after admission i e during the presence and healing period of the acute myocardial lesion It must not pass unnoticed that the mortality rate increased along with a decreasing J point and with the number of lead sets showing the pattern Clinical studies on exercise stress ECG have shown that the degree of ST segment depression in stress is related to the severity of coronary artery disease[24-26] Our results also support certain previous experiences gathered in the Coronary Drug Project,[27] although their definition of the ST segment depression slightly differed from ours

Summary

An ST segment depression was studied in the ECGs recorded on the first and third day after admission of 580 patients with an acute heart attack An acute myocardial infarction was found in 86% of the 115 patients in whose ECG the J point was depressed 2 mm or more and the ST segment was horizontal or sloping downwards in at least one lead (a definite ST segment depression)

The degree of the J point depression was deemed of prognostic significance During the first four weeks the mortality rate was lowest (4 7%) in patients with a J point depression less than one millimeter or no depression The corresponding figure for patients with a definite ST segment depression was three times (21 7%) that of the patients without the pattern (7 3%)

The definite ST segment depression in an acute coronary attack seemed to be accompanied by a severe degree of coronary heart disease Significant differences between the patients with a definite ST segment depression and those without the pattern were found in the C/T ratio in the degree of pulmonary congestion in the ECG signs of LVH and in the digitalis treatment

It is concluded that the definite ST segment depression has an important clinical and prognostic significance in cases of acute coronary attacks

REFERENCES

1 Cook R W Edwards J F and Pruitt R D [illegible] cardiographic changes in acute subendocardial [illegible] tion Circulation 18 603 1958
2 Phillips J H DePasquale N I and Burch G [illegible] electrocardiogram in infarction of the anter[illegible] papillary muscle Am Heart J 66 338 1963
3 Rakita J Borduas J L Rothman S and Prin[illegible] M Studies on the mechanisms of ventricular [illegible] XII Early changes in the RS T segment an[illegible] complex following acute coronary artery oc[illegible] Experimental study and clinical application[illegible] Heart J 48 351 1954
4 Raunio H Rissanen V Romppanen T Jokin[illegible] Rehnberg S Helin M and Pyörälä K Change[illegible] QRS complex and ST segment in transmural and [illegible] docardial myocardial infarction A clinicopath[illegible] study Am Heart J 98 176 1979
5 Georas C S Dahlquist E and Cutts F B Su[illegible] cardial infarction Correlation of clinical, electro[illegible] graphic and pathologic data in 17 cases, Arch. [illegible] Med 111 488 1963
6 Heikkilä J Electrocardiography in acute papillar[illegible] cle dysfunction and infarction A clinicopath[illegible] study Chest 57 510 1970
7 Abbott J A and Scheinman M M Nondiag[illegible] electrocardiogram in patients with acute myo[illegible] infarction Clinical and anatomic correlations, [illegible] Med 55 608 1973
8 Turner A F Lau F Y K and Jacobson G A [illegible] for the estimation of pulmonary venous and a[illegible] pressures from the routine chest roentgenogram [illegible] 116 97 1972
9 Social Insurance Institution s Coronary Heart D[illegible] Study AL 1/1975 Helsinki 1974 Kansaneläkel[illegible] Julkaisuja
10 Myers G B Sears C H and Hiratzka T Corr[illegible] of electrocardiographic and pathologic findings [illegible] like subendocardial infarction of the left ventricle [illegible] Med Sci 222 417 1951
11 Vincent G M Abildskov J A and Burgess [illegible] Mechanism of ischemic ST segment displacement. [illegible] uation by direct current recordings, Circulation [illegible] 1977
12 Surawicz B and Saito S Exercise testing [illegible] tion of myocardial ischemia in patients with abn[illegible] electrocardiograms at rest Am J Cardiol [illegible] 1978
13 Case R B Roselle H A and Cramp[illegible] Relation of S T depression to metabolic and he[illegible] namic events Cardiologia 48 32 1966
14 Raunio H Unpublished findings
15 Timogiannakis G Amende I Martinez F and T[illegible] as M ST segment deviation and regional myo[illegible] blood flow during experimental partial coronary a[illegible] occlusion Cardiovasc Res 8 469 1974
16 Kjekshus J K Maroko P R and Sobel B[illegible] Distribution of myocardial injury and its relat[illegible] epicardial ST-segment changes after coronary a[illegible] occlusion in the dog Cardiovasc Res 6 490 19[illegible]
17 Madias J E and Hood W B Precordial ST[illegible] mapping 4 Experience with mapping of ST[illegible] depression in anterior transmural myocardial in[illegible] J Electrocardiol 9 (4) 31 1976
18 Ross J Electrocardiographic ST segment and [illegible] the characterization of myocardial ischemia and [illegible] tion Circulation 53(Suppl) I 73 1976
19 Jelides L J Reid D S Thomas M and S[illegible] I Inhibition by β blockade of the ST-segment ele[illegible]

after acute myocardial infarction in man Cardiovasc Res. 6 295 1972.

20 Bruyneel, K. J J Use of moving epicardial electrodes in defining ST segment changes after acute coronary occlusion in the baboon. Relation to primary ventricular fibrillation AM HEART J 89 731 197ɔ

21 Kato K., Fukuda, H., and Koyama S *Depression of the* ST-segment in epicardial electrocardiogram associated with experimental major coronary artery constriction J Electrocardiol. 1(2) 167 1968.

22. Krotkiewski, A Cajewska Lipka, J., Szelemetko J., and Ruszkowski, J Multi lead electrocardiogram in relation to serum enzymes in acute myocardial infarction Br Heart J 35 991 1973.

23 Ekmekci, A Toyoshima H., Kwoczynski, J K., Nagaya T and Prinzmetal M Angina pectoris IV Clinical and experimental difference between ischemia with S-T elevation and ischemia with S-T depression, Am. J Cardiol. 7 412, 1961

24. Bartel, A. G., Behar V S., Peter R. H., Orgain, E. S., and Kong Y *Graded excercise stress tests in angiographically* documented coronary artery disease Circulation 49 348 19"4.

25 Martin, C M., and McConahay D R. Maximal treadmill excercise electrocardiography Correlations with coronary arteriography and cardiac hemodynamics, Circulation 46 9.6 19"2.

26 Kurita, A., Chaitman, B R., and Bourassa, M G Significance of exercise-induced junctional S-T depression in evaluation of coronary artery disease Am. J Cardiol. 40 492, 19""

27 The Coronary Drug Project The prognostic importance of the electrocardiogram after myocardial infarction, Ann. Intern. Med. 77 6"" 19"2.

Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978 Therefore all manuscripts must be accompanied by the following written statement signed by one author The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C V Mosby Company in the event the work is published The undersigned author warrants that the article is original is not under consideration by another journal and has not been previously published I sign for and accept responsibility for releasing this material on behalf of any and all co-authors Authors will be consulted when possible regarding republication of their material.

Low dose heparin in the prevention of deep-vein thromboses in patients with acute myocardial infarction

Aubrey Pitt M D F R A C P
Stanley T Anderson F R A C P
Peter G Habersberger F R A C P
David S Rosengarten F R A C S
Melbourne Australia

The radioactive fibrinogen test has been shown to accurately detect lower limb deep vein thrombosis[1-8] Studies in patients with acute myocardial infarction using this technique have indicated an incidence of venous thrombosis of 29% to 38%[9-13] Anticoagulants have been shown to significantly reduce the frequency of leg vein thrombosis and pulmonary embolism after acute myocardial infarction[3,4] In postoperative patients where the incidence of deep vein thrombosis is of the same order as after myocardial infarction low doses of heparin have been shown to be as efficacious as full anticoagulation in decreasing the incidence of deep vein thrombosis[15] and fatal thromboembolism

In a previous report from this department[20] the incidence of venous thrombosis in a fully anticoagulated group of patients with acute myocardial infarction was 9 4% and not significantly different from the 12 7% incidence in patients given 1 000 units of heparin by intravenous infusion daily for 48 hours This report is of a second trial and presents the incidence of leg vein thrombosis in patients with myocardial infarction and compares a control group with two anticoagulant regimes one using a low dose of intravenous heparin and the other full anticoagulation using heparin and warfarin sodium The influence of cardiac failure in promoting venous thrombosis is also presented

From the Cardiovascula Diagn st Serv e Alf ed Hosp tal Mel bourn Australia
Received for publication Sep 1979
Accepted for publication No 26 1979
Reprint requests Dr Aubrey Pitt Alfred Hosp t l Comm rcial Road M lbourne 3181 Australia

Patients and methods

All patients with a myocardial infarction than 48 hours duration were considered fo sion in the trial unless there was contraind to anticoagulants where the patient was on anticoagulants or if cardiogenic sho present since these patients were unli survive the duration of the trial period

One hundred and fifteen patients enter trial and of these seven were withdrawn because of death before completion of th period three due to technical problems w counting equipment and one because the ing physician requested a change in the ant ulation regime There were no instances o vein thrombosis or pulmonary embolism patients withdrawn from the trial

Patients were randomized into one of groups by the drawing of a sealed envelo fully anticoagulated group typically 5 000 units of heparin intravenously as a lo dose and then 20 000 units by intravenous sion every 12 hours for 48 hours the dose adjusted to maintain a whole blood clott between 30 and 90 minutes These patients also given warfarin sodium on admission a was continued after the cessation of hepa sufficient dosage to maintain the prothro index between 10% and 35% A low dose hep group were given 500 units of heparin dextrose by intravenous infusion every 12 for 48 hours The control group received 5% dextrose by intravenous infusion for days No anticoagulants were given to the two groups after cessation of intravenous th py

0002-8703/80/050574 + 0$00 50/0 © 1980 The C V Mosby

On admission to the coronary care unit patients were given sodium iodide intravenously followed by oral potassium iodide so as to block thyroid gland uptake of radioiodine One hour after the administration of sodium iodide 200 microcuries of ¹²⁵I labelled fibrinogen was given intravenously Using a Pitman portable scintillation counter counts were made daily over the precordium and on eight sites on each leg for 7 to 10 days The legs were elevated to 15 degrees for at least 5 minutes prior to counting The leg counts were expressed as a percentage of the precordial count a difference of more than 15% between adjacent sites on the calf or between identical positions on each leg was accepted as evidence of a venous thrombosis

Patients were permitted to use a bedside commode but were otherwise confined to bed during the study period All patients undertook active leg and breathing exercises daily under the supervision of nursing staff Daily examination was made of the legs to ascertain if clinical signs of venous thrombosis were present

Patients were also assessed as to the presence or absence of cardiac failure which was diagnosed if there was a third heart sound basal moist sounds not clearing on coughing or evidence of pulmonary venous congestion on a chest x ray which was taken daily for 3 days Statistical analyses were made with the Fisher exact probability test

Results

Thirty seven patients were in the control group 36 in the low dose heparin group and 35 in the fully anticoagulated group The average age of patients in each group was similar The control and fully anticoagulated groups showed a similar preponderance of males while there were only three females in the low dose heparin group Mean admission time after infarction was slightly longer in the fully anticoagulated group The mean SGOT was slightly lower in the control group compared with either treatment group (Table I) The groups were not significantly different when height weight body surface area or site of infarction as determined by ECG were compared

The frequency of venous thrombosis (Table II) was 29 7% in the control group 13 9% in the low dose heparin group and 11 4% in the fully anticoagulated group The difference between either of the treatment groups when compared with the control group was significant ($p < 0.05$) but

Table I

	Control	*Lou dose heparin*	*Fully anticoagulated*
Mean age (years)	56 9	54 4	56 2
Sex M	30	33	27
F	7	3	8
Mean admission time (hours) after infarction	7 8	7 1	9.5
Mean S G O T	193	232	225

Reitman Frankel units.

Table II

	No of patients	*Venous thrombosis*	*% incidence*
Control	37	11	29 7
Low dose heparin	36	5	13 9
Fully anticoagulated	35	4	11 4

there was no significant difference between treatment groups

When divided according to the presence or absence of cardiac failure there was a slight preponderance of patients with failure in the fully anticoagulated group compared with the control and low dose heparin patients (Table III) No significant differences were present in age or admission time after infarction Patients with failure had higher mean peak SGOT levels compared with patients with no failure

In the control group the patients with cardiac failure had a significantly higher incidence of venous thrombosis when compared to patients with no failure ($p < 0.02$) (Table IV) In the low dose heparin group and in the fully anticoagulated group there was no significant difference between patients with and without cardiac failure In patients without cardiac failure there was no significant difference between the control and either treatment groups Conversely in patients with cardiac failure control patients had a significantly higher incidence of venous thrombosis when compared with the low dose heparin group ($p < 0.05$) or the fully anticoagulated group ($p < 0.02$) but the two treatment groups were not significantly different

Of the 20 patients with venous thrombosis seven were persistent lasting 48 hours or more and 13 were transient The right leg was involved in nine patients the left in five and six were bilat

Table III

	Control		Low dose heparin		Fully anticoag...	
	No CCF	CCF	No CCF	CCF	No CCF	CC[illegible]
No of patients	30	7	27	9	21	[illegible]
Mean (years)	56 6	57 4	53 3	57 8	55 7	[illegible]
Mean S G O T	196	225	205	311	18	[illegible]
Mean admission time (hours) after infarction	8.3	5 1	7 5	6 0	9.3	[illegible]

CCF = cardiac failure
Reitman Frankel units

Table IV

		No of patients	Venous thrombosis	% incidence
Control	No CCF	30	6	20 0
	CCF	7	5	71 4
Low dose heparin	No CCF	27	4	14.8
	CCF	9	1	11 1
Fully anticoagulated	No CCF	21	3	14.3
	CCF	14	1	7 1

CCF = cardiac failure

eral No trend was apparent in the persistence or otherwise of venous thrombosis in the different treatment groups The time of diagnosis of the venous thrombosis varied between 1 and 8 days after admission the average being 4 5 days Again no difference was apparent in the different groups Venous thromboses were confined to below the knee and in no patient was the thrombus observed to extend above midthigh In only one patient was there clinical evidence of a venous thrombosis and no patient suffered a clinical pulmonary embolus

Discussion

The incidence of venous thrombosis of the legs in the control patients was 29 7% and is similar to the previously reported incidence of venous thrombosis in acute myocardial infarction and also in postoperative patients Several reports have confirmed that anticoagulation reduces the frequency of venous thrombosis in patients with infarction from 38 to 5 5% using 40 000 units of heparin by intravenous infusion daily with oral anticoagulants from 29% to 0% using 40 000 units of heparin adjusted to maintain whole blood clotting time between 2½ and 3 times normal The Medical Research Council reported a diminished frequency of thromboembolism in patients receiving full anticoagulation using heparin and phenindione compared with a control group of low dosage phenindione but the diagnosis of events was made on clinical grounds only

Low dosage heparin has been reported to reduce the incidence of venous thrombosis in postoperative patients when the labelled fibrinogen technique has been used to detect this complication Using aqueous calcium heparin a dose of 5 000 units subcutaneously every 12 hours Kakkar and colleagues[17] demonstated a reduction in incidence from 26% in controls to 4% in treated patients Similarly Gordon Smith and colleagues[18] used 5 000 units of subcutaneous sodium heparin every 12 hours for three doses or 5 days and both groups had a lower incidence (13.5% and 8 3%) of venous thrombosis compared with controls (42%) Nicolaides and associates[19] used 5 000 units subcutaneously every 12 hours for 5 days and had an incidence of 0 8% compared with [illegible] in the control group Gallus and co workers using 5 000 units of heparin subcutaneously three times daily reduced the incidence from 16% to 1 9% after elective surgery and from 48% to [illegible] after hip fracture

We have previously reported a trial comparing two regimes of anticoagulants in effecting the incidence of venous thrombosis in patients with acute myocardial infarction Low dose heparin (1 000 units daily) was not significantly different from a therapeutic regime of full heparin dosage (controlled by whole blood clotting time) and warfarin sodium (controlled by prothrombin index) the incidence being 12 7% and [illegible] respectively The present trial extends these results and confirms that a low dose heparin and a fully anticoagulated group have significantly less venous thrombosis than do control patients on no anticoagulants In both trials the fully anticoagulated group showed a slightly lower incidence than the low dose heparin group but the differences were not statistically significant

When the results of the current trial are further examined to determine the difference in incidence of venous thrombosis in patients with and without cardiac failure there was inequality of numbers of patients in each group but those with cardiac failure on no therapy had a significantly higher incidence than did patients without failure That patients with cardiac failure have a higher incidence of venous thrombosis is not surprising as it is well established that venous stasis is a predisposing cause of venous thrombosis[2] In the two treatment groups statistical significance was not obtained when patients with and without failure were compared nor was there a difference in the three groups in patients without failure Hence if these figures are confirmed by further trials anticoagulants have their major prophylactic role in patients with cardiac failure and very low dose heparin may confer the same benefit as full dosage of anticoagulants

Previous reports in the literature have also shown that patients with cardiac failure have an increased frequency of venous thrombosis Maurer and colleagues found a higher incidence of venous thrombosis in patients with a myocardial infarction complicated by left ventricular failure or cardiogenic shock compared with uncomplicated patients but the differences did not reach statistical significance Miller and co workers in studying the effect of early ambulation on the incidence of venous thrombosis showed a significant increase in incidence in those patients with failure who were confined to bed Kotilainen and associates found an increased incidence in patients with cardiac failure however this did not reach statistical significance if patients with cardiogenic shock were excluded Cristal et al using a modified coronary prognostic index showed a significant difference in venous thrombosis when comparing patients in good clinical condition with those who were severely ill

Handley showed no difference in the incidence of deep vein thrombosis after myocardial infarction when 26 patients given low dose subcutaneous heparin were compared with 24 control patients However the frequency of cardiac failure and the admission time after infarction were not indicated The former as shown in this report is associated with a high incidence of venous thrombosis and if one group were weighted with a larger number of patients with failure and two groups may not be comparable Further as Handley suggests low dose heparin prophylaxis may not be effective if given some time after the event initiating the venous thrombosis but he does not state the admission time of his patients In the present trial only patients with a myocardial infarct of less than 48 hours duration were accepted and the average admission time was less than 10 hours in each of our three groups Kotilainen and colleagues used only oral anticoagulant therapy with warfarin sodium and as these may not be effective in preventing development of thrombi during the first 3 to 5 days these authors showed a relatively high incidence overa all of 21%

In the currently reported series patients were confined to bed (apart from use of a bedside commode) for the duration of the study Miller and colleagues have demonstrated a significant reduction associated with early mobilization The utilization of very low dosage heparin intravenously for the initial 48 hours together with early mobilization would seem to offer the greatest benefit with the least risk

The labelled fibrinogen technique is only useful in the detection of calf vein and low thigh thrombosis and has little diagnostic capability for femoral vein thrombosis above midthigh. There is evidence that thromboses limited to the calf have a lower risk of leading to pulmonary embolism Conversely there have been reports of pulmonary emboli in patients with thrombosis apparently confined to the calf [3] In any case in a clinical study Sharnoff and de Blasio[1] reported a lower incidence of fatal thromboembolism in a group of operative patients receiving prophylactic heparin compared with controls

The possible mode of action of low dose heparin remains speculative There is evidence that heparin may potentiate the activity of a naturally occurring inhibitor to activated factor X[17,23,3] Small doses of heparin may be adequate before tissue trauma activates factor X but if given later larger doses of heparin are required to reduce enhanced platelet stickiness that is observed following surgery[3] and myocardial infarction[2] O Brien[31] has recently reviewed the possible modes of action of heparin in preventing venous thrombosis

Summary

Patients with acute myocardial infarction of less than 48 hours duration were randomized into three groups The fully anticoagulated group received heparin by intravenous infusion and warfarin sodi

um to maintain a whole blood clotting time of 30 to 90 minutes and a prothrombin index of 10% to 35% The low dose heparin group received 500 units by intravenous infusion every 12 hours The control group received no anticoagulants The radioactive fibrinogen test was used to diagnose the presence of leg vein thromboses

The control group had an incidence of venous thrombosis of 29 7% compared with 13 9% in the low dose group and 11 3% in the fully anticoagulated group Patients in the control group who had cardiac failure had a significantly higher incidence of venous thromboses (71 4%) when compared with patients not in failure (20 0%) In the two treatment groups no significant difference was observed in patients with and without cardiac failure

Patients with cardiac failure complicating an acute myocardial infarction have a high incidence of venous thromboses Anticoagulants significantly reduce this incidence and low dose intravenous heparin is as efficacious as full anticoagulation

REFERENCES

1 Negus, S., Pinto D Le Quesne L P Brown N., and Chapman M I labelled fibrinogen in the diagnosis of deep-vein thrombosis and its correlation with phlebography Br J Surg 55 835 1968
2 Flanc C Kakkar V V and Clarke M B The detection of venous thrombosis of the legs using I labelled fibrinogen Br J Surg 55 742, 1968
3 Kakkar V V Flanc C and Tsapogas, M J Role of phlebography in deep-vein thrombosis, Br J Surg 55 [illegible] 1968
4 Palko P D Nanson E M and Fedoruk, S D The early detection of deep venous thrombosis using I tagged human fibrinogen Can J Surg 17 215 1964
5 Lambie J M Mahaffy R G Barber D C Karmody A M Scott M M and Matheson N A Diagnostic accuracy in venous thrombosis, Br Med J 2 142, 1970
6 Atkins P and Hawkins L A Detection of venous thrombosis in the legs Lancet 2 1217 1965
7 Mason E M Palko P D Dick A. A. and Feddruk, S O Early detection of deep venous thrombosis of the legs using I tagged human fibrinogen Ann Surg 162 438, 1965
8 Atkins, F and Hawkins, L A The diagnosis of deep-vein thrombosis in the leg using I fibrinogen Br J Surg 55 [illegible] 1968
9 Murray T S Lorimer A R Cox F C and Lawrie T D V Leg vein thrombosis following myocardial infarction Lancet 2 [illegible] 1970
10 Nicolaides, A N Kakkar V V Renney J T G Kinder P H Hutchison D C N and Clark, M B Myocardial infarction and deep-vein thrombosis, Br Med. J 1 432, 1971
11 Maurer B J Wray R and Shillingford J P Frequency of venous thrombosis following myocardial infarction Lancet 2 1385 1971
12 Maurer B J., The incidence of venous thrombosis after myocardial infarction Q J Med 39 630 1970
13 Handley A. J., Emerson P A., and Fleming P R Heparin in the prevention of deep vein thrombosis in myocardial infarction, Br Med. J 2 436 1972
14 Medical Research Council Assessment of short-term anticoagulant administration after cardiac infarction Br Med J 1 335 1969
15 Nicolaides A N Dupont P A., Desai, S., Lewis, J. D., Douglas, J N Dodsworth H., Founde, G Luck R and Jamieson C W Small doses of subcutaneous sodium heparin in preventing deep venous thrombosis after major surgery Lancet 2 890 1972
16 Gordon Smith I C Grundy D J Le Quesne L P Newcombe J F., and Bramble F J Controlled trial of two regimens of subcutaneous heparin in prevention of postoperative deep vein thrombosis, Lancet 1 [illegible] 1972
17 Kakkar V V Field E S., Nicolaides, A. N Flute P T Wessler S., and Yin E T Low doses of heparin in prevention of deep-vein thrombosis, Lancet 2 669 [illegible]
18 Gallus A S., Hirsh, J., Tuttle R J Trebilcock R O Brien S E., Carroll J J Minden J H and Hudecki S M Small subcutaneous doses of heparin in prevention of venous thrombosis, N Engl. J Med. 288 545, 1973
19 Sharnoff J G and de Blasio G Prevention of fatal postoperative thromboembolism by heparin prophylaxis Lancet 2 1006 1970
20 Habersberger P G Pitt A., and Anderson, S. T Venous thrombosis in myocardial infarction. Comparison in heparin dosage Br Heart J 35 538 1973
21 Rosengarten D S., Laird J., Jeyasingh, K and [illegible] P The failure of compression stockings to prevent deep venous thrombosis after operation, Br J Surg 57 [illegible] 1970
22 Beeson P B., and McDermott, W Pulmonary embolism and infarction in Cecil R. L. F., and Loeb R F eds Cecil Loeb Textbook of Medicine Philadelphia 1967 W B Saunders Company p 534
23 Miller R R. Lies, J E Carretta R. F., Wampold D E De Nardo G L., Kraus, J F., Amsterdam E A., and Mason D T Prevention of lower extremity venous thrombosis by early mobilization Ann. Intern. Med 84 700 1976
24 Kotilainen M Ristola, P Ikkala E and Pyorala K Leg vein thrombosis diagnosed by [illegible] fibrinogen test after acute myocardial infarction Ann. Clin. Res 5 365 1973
25 Cristal, N., Stern, J., Ronen, M Silverman, C., Ho [illegible] and Bartov E Identifying patients at risk for thromboembolism JAMA 236 2355 1976
26 Handley A. J Low-dose heparin after myocardial infarction Lancet 2 623 1972
27 Kakkar V V., Howe C T Flanc C and Clarke M B Natural history of postoperative deep-vein thrombosis Lancet 2 230 1969
28 Browse N. L. The problems of deep vein thrombosis Am Heart J 84 149 1972
29 Yin E T., Wessler S and Stoll P J [illegible] properties of the naturally occurring plasma inhibitor activated Factor X J Biol Chem. 246 3703, 1971
30 Biggs R., Denson K. W E Akman N Barrett R Hodden M Antithrombin III antifactor Xa and heparin Br J Haematol. 19 283, 1970
31 Negus, D., Pinto D J and Slack W W Effect of small doses of heparin on platelet adhesiveness and lipoprotein lipase activity before and after surgery Lancet 1 [illegible] 1971
32 McDonald L., and Edgill, M Coagulability of the blood in ischaemic heart disease Lancet 2 45 19[illegible]
33 O Brien J R. Heparin platelets, and venous thrombosis Am Heart J 85 435 1973

Captopril in severe treatment-resistant hypertension

Roger K Ferguson M D
Peter H Vlasses Pharm D
Janice R Koplin R N
Anne Shirnman B S
James F Burke Jr M D
John C Alexander M D
Philadelphia Pa

True resistance of the blood pressure to conventional therapy is an uncommon but serious problem in the management of hypertensive patients[1] After factors such as poor patient compliance and excessive dietary sodium have been eliminated approximately 3 to 5% of patients are uncontrolled by various combinations of standard antihypertensive drugs[2] Studies in such patients suggest that a high peripheral vascular resistance persists despite drug therapy and may account for the blood pressure elevation[3] Moreover antihypertensive drugs may actually induce reactions such as fluid retention and elevated plasma renin activity[4, 5] that may raise blood pressure Unfortunately even when effective these agents can produce undesired effects which limit their use

Captopril, an orally active angiotensin converting enzyme inhibitor is currently being investigated for the treatment of various forms of hypertension[6, 7] It is believed to act primarily by blockade of the conversion of angiotensin I to angiotensin II[8] although other mechanisms have been postulated The purpose of the present study was to compare captopril alone or in combination with the highly effective regimen[10] of diuretic propranolol and hydralazine in the treatment of resistant hypertension Captopril in combination with a diuretic or a diuretic and beta adrenergic blocking agent offered therapeutic advantages to the standard three drug regimen in a majority of our patients In some patients however captopril s use was limited by side effects

Materials and methods

Patients To be eligible for the study a patient had to have a history of supine diastolic blood pressure (SDBP) exceeding 120 mm Hg and had to have failed on conventional drug therapy i.e SDBP between 100 and 120 mm Hg or to have intolerable side effects from these agents Men and women who fit these criteria gave written informed consent to participate in this study Their mean age was 48 years with a range of 17 to 70 years

An assessment of the etiology of the hypertension and the presence and degree of end organ involvement was made after a thorough history, physical and laboratory evaluation including renal scan or arteriography when indicated. The diagnosis of renovascular hypertension was based on the demonstration of significant stenosis of a renal artery associated with increased renal vein renin activity on one side or two to threefold increases peripherally All patients were advised to follow moderate (75 to 100 mEq /day) sodium restriction throughout the study

Design of study During a prerandomization period each patient was placed on standard triple therapy (STT) consisting of hydrochlorothiazide 100 mg /day or furosemide 80 to 120 mg /day propranolol 320 mg /day and hydralazine 200

From the Departments of Medicine and Pharmacology Jefferson Medical College of Thomas Jefferson University Philadelphia, Pa.

Received for publication Sept 26 1979
Accepted for publication Nov 27 1979

Reprint requests Roger K Ferguson, M D Clinical Pharmacology Division M-502, Thomas Jefferson University Hospital, Philadelphia, Pa. 19107

Table 1 Characteristics and changes in blood pressure and heart rate of severely hypertensive patie[illegible] before and after captopril (CAP) alone and in combination with diuretic (DIU) and propranolol (PPC

Patient No	Age/Sex/Race	Diagnosis/End Organ Involvement	No of Drugs	Supine							
				Pre-STT		STT		CAP		CAP + [illegible]	
				BP	HR	BP	HR	BP	HR	BP	[illegible]
Group 1											
1	34 FB	EH LVH Grade II	3	150/106	84	170/114	78	160/110	84	130 84	[illegible]
2	51 FB	RVH LVH stroke Grade I	5	210/112	68	198/168	68	172/116	90	112/78	[illegible]
3	58 MW	RVH CAD Grade I	5	212/114	56	210/118	75	190/106	78	200 86	[illegible]
4	4[illegible] FB	EH LVH Grade I	5	192/122	72	160/112	78	182/116	84	132/90	[illegible]
5	42 FB	RVH LVH RI Grade II	4	154/110	54	168/118	72	164/108	96	104 68	[illegible]
6	61 MW	RVH CAD RI Grade I	3	220/108	80	200/100	80	178/86	78	190/98	[illegible]
Group 2											
7	58 MW	RVH LVH Grade I	5	150/98	50	220/110	52	175/96	56	190/10[illegible]	[illegible]
8	38 MW	MH IH LVH RI Grade IV	7	190 116	64	204/108	68	168/118	80	150/106	[illegible]
9	17 FW	EH RI Grade I	6	180/120	98	164/124	60	172/130	–	154/110	[illegible]
10	55 MB	EH LVH RI Grade II	5	260/110	78	240/112	72	1[illegible]0/104	88	174/108	[illegible]
11	30 MB	EH LVH RI Grade I	3	172/124	72	200/146	72	208/138	[illegible]6	190 138	[illegible]
12	61 FB	EH LVH RI Grade III	3	230/150	76	212/112	72	250/112	68	180/10[illegible]	[illegible]
13	63 MW	RVH LVH Grade I	3	240/140	64	220/120	60	194/120	80	198/108	[illegible]
14	50 MB	EH LVH Grade I	3	196/120	76	184/122	76	158/112	68	164/110	[illegible]
Group 3											
15	[illegible]0 FB	EH LVH Grade II	3	242/114	68	220/120	68	212/128	120	230/118	[illegible]
16	41 MB	EH LVH RI Grade II	4	240/155	42	246/136	52	232/132	64	188 138	[illegible]

EH = essential hypertension MH = malignant hypertension RVH = hypertension associated with renal artery stenosis LVH = left ventric[illegible] hypertrophy RI = renal impairment (serum creatinine > 2.2 mg/dL) Grade I IV = Keith Wagener Classification of retinopathy IH = intrac[illegible] bral hemorrhage

Patient No seven received metoprolol instead of propranolol.

†Refer to text fo drug doses and duration of each treatment.

mg/day Two patients could not tolerate hydralazine because of previous lupus-like reactions one took prazosin in place of hydralazine

If after 2 to 3 weeks on this regimen a patient s SDBP remained between 100 and 120 mm Hg he or she was admitted to the hospital and randomly assigned to either begin treatment with captopril or to continue STT for an additional period For those assigned to captopril it was initiated in a single dose of 25 mg and depending on response increased in a stepwise fashion to 150 mg If SDBP did not decrease at least 10 mm Hg the patient was considered an early treatment failure and was dropped from the study otherwise he or she was discharged for further follow up If the pressure was not controlled by captopril alone within a week, a diuretic was added after another 1 to 2 weeks if the pressure remained uncontrolled for a week, a beta blocker was then added

All patients who were randomized to continue STT subsequently had uncontrolled blood pressure within 2 to 6 weeks after discharge Wh[illegible] this occured the STT was stopped and cap[illegible] was initiated One patient with malignant hyp[illegible]tension and a SDBP > 120 mm Hg and a[illegible] with SDBP > 145 mm Hg despite STT were [illegible] randomized but were treated with captopril [illegible] emergency basis

After discharge patients were seen [illegible] every 3 to 4 days then weekly and then [illegible] throughout the 3 months of the study At ea[illegible] visit supine and standing blood pressure [illegible] pulse rate were recorded and possible adver[illegible] effects were assessed Pill counts and cha[illegible] medication dosage were made at each visit [illegible] new medication was dispensed The study pro[illegible] col was approved by the institution s Comm[illegible] on Research

Laboratory and safety assessment. B[illegible] counts urinalysis and standard labora[illegible] studies were done at specified intervals thro[illegible]

		Standing									
*AP + DIU + PROP**		*Pre-STT*		*STT*		*CAP*		*CAP + DIU*		*CAP + DIU + PROP**	
BP	*HR*	*BP*	*HR*	*BP*	*HR*	*BP*	*HR*	*BP*	*HR*	*BP*	*HR*
		154/110	88	164/118	84	156/116	88	128/92	90		
		210/114	74	196/108	74	154/112	108	108/72	120		
		210/118	60	2?0/108	74	198/108	88	196/92	92		
		170/118	68	156/110	72	176/114	82	13?/90	88		
		130/108	54	146/122	80	168/124	112	98/74	116		
		200/106	84	200/106	84	180/104	78	178/94	68		
168/90	60	138/88	52	212/112	56	160/96	52	180/104	84	138/80	60
122/85	82	170/105	68	198/134	68	168/118	84	14?/104	102	110/86	98
150/92	84	140/90	92	130/105	92	182/140	—	156/118	104	146/90	94
168/94	52	190/110	80	200/120	74	168/118	80	175/122	86	140/90	52
136/92	64	180/130	76	200/150	72	194/142	76	158/120	110	133/98	74
178/106	76	220/145	80	200/110	76	218/110	68	186/100	72	164/98	98
160/106	64	230/136	64	220/124	64	174/128	68	189/118	72	1?0/100	56
134/90	58	194/128	68	174/120	92	176/118	72	148/108	88	140/96	72
220/120	76	234/110	72	248/130	72	200/114	64	200/112	124	240/118	72
230/124	60	240/150	60	230/124	64	240/138	72	18?/136	?8	200/120	68

ut the study An electrocardiogram (ECG) was one before and during the study Careful phthalmoscopic evaluation was performed at he beginning of the study and again after 3 nonths Plasma renin activity (PRA) was measured by radioimmunoassay[11] before starting captopril and subsequently after stabilization on a iven regimen Normal values (mean ± 1 SD) on 100 mEq Na diet are 1 6 ± 0 4 ng /ml /hr

Statistical methods Blood pressures and heart ates used in the analysis represent the values btained at the last visit before a protocol pecified change in the treatment regimen Group neans are presented with the standard error of he mean as the index of dispersion Student s *t* est for paired observations was used for analysis f the data A p value of less than 0 05 was onsidered significant

esults

Patient characteristics Sixteen patients nine nen and seven women aged 17 to 70 (mean 48 ears) entered the study (Table I) Another oman with renovascular hypertension developed a skin rash after the first dose of captopril and could not complete the protocol her data are excluded Most had essential hypertension (EH) one (No 8) in the malignant stage The diagnosis of renovascular hypertension was made in three patients (No 3 5 and 6) and was strongly suspected in 3 others (No 2 5 and 13) on the basis of renal scan and PRA Fourteen of the patients had ECG evidence of left ventricular hypertrophy (LVH) Eight had significant renal impairment (serum creatinine > 2 4 mg /dl) primarily due to nephrosclerosis in one patient (No 9) hemolytic uremic syndrome was the initiating cause of the renal insufficiency

Despite taking an average of four antihypertensive drugs (range 3 to 7) prior to entering the study the patients had unsatisfactory blood pressure control and in many cases side effects from the medications. The mean SDBP on these drugs was 207/120 ± 12/5 mm Hg while the supine heart rate (HR) was 69 ± 3 beats/minute When placed on *STT* in the prerandomization period the mean SDBP was 201/118 ± 7/3 mm Hg the HR on this regimen was 70 ± 3 beats/minute

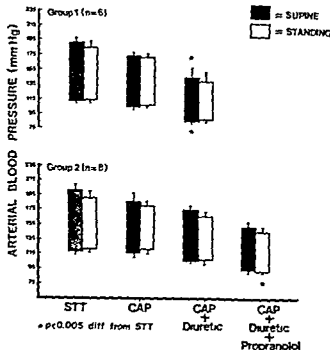


Fig 1 Supine and standing blood pressure responses to captopril (*CAP*) alone or in combination in hypertensive patients uncontrolled by standard triple therapy (*STT* = diuretic, propranolol and hydralazine) Refer to text for explanation of groups and doses

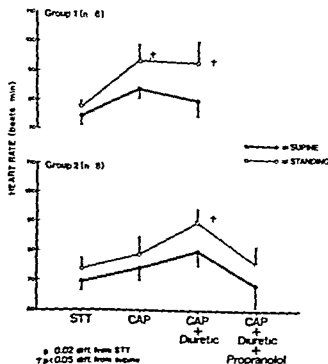


Fig 2. Supine and standing heart rate responses to captopril (*CAP*) alone or in combination compared to standard triple therapy (*STT* = diuretic propranolol and hydralazine) Refer to text for groups and doses

Mean PRA on STT just prior to starting cappril was 9 8 ± 2 1 ng /mL/hr

Response to captopril All 16 patients ... captopril since even the patients who ... to STT eventually failed In the hospital ... stopping STT the SDBP was 195/116 ± 6/3 ... Hg the initial 25 mg captopril dose prod... mean maximal fall of 36/19 ± 5/3 mm Hg ... response occurred at 15 minutes to 1 ho... drug administration and lasted 2 to 4 hours ... magnitude of the response was not enh... larger single doses (up to 150 mg) of ca... but the duration of the blood pressure ... was prolonged sometimes for as long as 6 ... hours All patients had more than a 10 mm ... fall in pressure but none became symptom...

As the effects of STT wore off no patient ... be controlled on captopril alone (up to 600 ... day) and there was no correlation ... initial and sustained blood pressure resp... The sustained response to captopril for th... patients averaged SDBP 188/115 ± 7/3 ... with a HR of 80 ± 4 beats/minute Since ... blood pressure was not controlled an oral d... and if necessary, a beta adrenergic block... agent was then added (see below)

Group 1 Six of the 16 patients (Fig. 1 *top*) ... controlled with captopril plus an oral di... usually hydrochlorothiazide 50 to 100 mg ... One patient (No 6) with reduced renal fu... later required furosemide in place of hydroc... thiazide mainly to control edema SDBP ... regimen was 143/85 ± 14/4 mm Hg wh... significantly less ($p < 0.05$) than the blood pres... sure on STT and captopril alone There was ... significant difference between lying and sta... blood pressures in this group for any tre... ment

Supine HR (Fig 2 *top*) on captopril al... captopril plus diuretic was not different fro... on STT however the standing HR on each ... these two treatments was significantly (p < ... higher than that on STT Likewise sta... on these treatments was greater than sup... ($p < 0.02$) and in two patients (No 2 a... reached 108 beats/minute or higher

PRA on captopril and diuretic was 5... ng /mL/hr compared to 8 9 ± 3 ng /mL/h... STT

Group 2 In another group of eight pa... (Fig 1 *bottom*) the addition of propra... necessary to control blood pressure or bec...

n this group captopril alone had produced a decrease in SDBP comparable to that of STT viz 187/116 ± 11/5 mm Hg Addition of hydrochlorothiazide or furosemide produced only a slight decrease in SDBP to 175/111 ± 6/4 mm Hg The addition of propranolol (40 to 80 mg /day) or metoprolol (150 mg /day) in one patient further reduced the SDBP to 152/94 ± 7/3 mm Hg which was significantly different ($p < 0.005$) from STT There was no significant postural change in blood pressure for any treatment in this group

Standing HR was higher during treatment with captopril ($p < 0.05$) and diuretic than with STT ($p < 0.02$) In addition a significant difference between supine and standing HR only occurred in the same regimen patients No 8 and 9 had HR increases to greater than 100 beats/minute and were symptomatic Propranolol (40 mg /day) was effective in controlling both HR and symptoms in the latter two patients

PRA on this regimen was 38 ± 14 ng /ml /hr compared to 11 ± 3 ng /ml./hr on STT

Group 3 The blood pressure of two patients (No 15 and 16) in spite of an initial good response to captopril alone could not be subsequently controlled by captopril diuretic and propranolol in maximal doses They were then classified as treatment failures even though SDBP decreased slightly from 233/128 mm Hg on STT to 225/122 mm Hg on this new regimen

PRA for these two patients were 2 1 and 24 5 ng /ml /hr compared to 0 7 and 4 1 on STT

Adverse effects on captopril Five of the original 17 patients developed a pruritic maculopapular skin rash In one woman this occurred after the first dose and required stopping the drug in the other patients it occurred after several weeks of captopril (mean dose 450 mg /day) In patients No 9 and 10 the rash resolved after 7 to 10 days in spite of the continuation of captopril although at a reduced dose In patients No 5 and 8 a mild rash has persisted but has not required discontinuation of captopril Patients No 7 and 10 also developed an abrupt loss of taste (ageusia) which lasted 6 weeks but spontaneously improved ANA titers did not increase after captopril

Two patients in Group 1 who had standing HR increases developed an acute myocardial infarction after 2 months of treatment In patient No 2 use of propranolol to control heart rate was considered but she was asymptomatic and had well controlled blood pressure In patient No 3 propranolol could not be added because it had contributed to previous episodes of pulmonary edema more frequent angina responsive to nitrates preceded his myocardial infarction Both these patients recovered without complications captopril was subsequently discontinued in patient No 2 as it was no longer needed to control her blood pressure

Patient No 11 developed severe postural hypotension shortly after adding furosemide to captopril but this subsequently resolved No other hemodynamic or laboratory abnormality was observed that could be attributed to captopril Five patients had 2 to 3+ proteinuria at the beginning of the study none of the others developed it while receiving captopril Serum creatinine did not change in any group ($p > 0.05$) and no changes were detected by slit lamp examination before and after treatment with captopril

Summary

The blood pressure of the majority of hypertensive patients can be controlled by sodium restriction and by one or at most two antihypertensive drugs When the blood pressure does not respond a widely recommended three-drug regimen is an oral diuretic propranolol and hydralazine [10] Our 16 patients had essential and renovascular hypertension and were refractory to all previous therapy The majority had end organ manifestations of severe hypertension such as left ventricular hypertrophy renal impairment retinopathy and neurologic sequelae When they were placed on STT their blood pressure remained uncontrolled (SDBP > 100 mm Hg) Because of the resistance of their blood pressure to STT all our patients were ultimately switched to captopril in an effort to achieve better control

According to the protocol patients were hospitalized after stopping STT the night before Captopril was started in a dose of 25 mg and increased according to the response After the first dose no patient had a symptomatic hypotensive response though one patient s SDBP did fall 60/30 mm Hg The maximum response to the initial dose usually occurred by 30 minutes rapid for an oral medication This initial response was often greater than the response to subsequent doses most likely due to the residual effects of STT It is controversial as to whether the pretreatment PRA is a predictor of the response to

captopril[7, 12] In our study it was not possible to determine PRA uninfluenced by drugs on a controlled sodium intake because of the severity of the hypertension PRA increased after captopril a response consistent with interruption of negative feedback inhibition of renin release[13]

As a group the patients' blood pressure on captopril alone approximated that on STT but no one was adequately controlled The addition of a diuretic enhanced the effectiveness of captopril and in six of the 16 patients it resulted in satisfactory blood pressure control Several of these patients who had hypertension in association with renal artery stenosis however manifested an upright tachycardia Worsening of angina pectoris occurred in one man and he and another woman developed subendocardial myocardial infarctions the role of the tachycardia in the precipitation of these events is unclear Nonetheless diuretic induced volume depletion with blockade of the renin angiotensin system by captopril may cause standing tachycardia, which may constitute a problem in patients with compromised coronary or cerebral circulation

In this regard two of the eight patients in Group 2 though well controlled on captopril and diuretic had propranolol added in small doses (40 mg /day) to control symptomatic standing tachycardia In the other six patients in this group blood pressure was normalized by this new three drug regimen and the regimen was well tolerated Two patients (Group 3) could not be controlled even with this regimen and were considered treatment failures It is of interest that propranolol produced additional blood pressure lowering in the presence of captopril which supports a hypotensive action of propranolol not due wholly to blockade of renin release[1]

In general captopril was well tolerated a number of patients remarked how much better they felt on captopril as compared to their previous regimens especially with regard to central side effects Five patients manifested a maculopapular and pruritic rash but in only one did discontinuation of captopril prove necessary In three patients the rash disappeared in 7 to 10 days with only a temporary reduction of captopril dosage Two men developed a loss of taste which similarly resolved despite continuation of captopril No other adverse effects have been noted in our patients Renal function was maintained as serum creatinine did not change during the study

Captopril induced proteinuria has been repor[illegible] since the start of our study[14] but could not b[illegible] documented retrospectively in our patients. H[illegible]ever continued surveillance of captopril's [illegible] effects especially proteinuria is necessary

In summary, in our three month trial, capto[illegible] appears to provide a useful and important al[illegible]native for the management of severe refra[illegible] hypertension Its mechanism of action seems [illegible] be ideal for such patients in whom the re[illegible] angiotensin system appears to play an impor[illegible] role Although alone it was insufficient to a[illegible]quately control the blood pressure in our sever[illegible] hypertensive patients its combination with [illegible] diuretic or a diuretic and a beta blocke[illegible] provided an effective and well tolerated combina[illegible]tion Nevertheless even with the latter thr[illegible] drug combination there were two treatme[illegible] fa[illegible]ures Adverse effects such as skin rash, wh[illegible] occurred in 30% of our patients and loss of ta[illegible] do not seem to seriously limit the use of the d[illegible] The development of a sustained standing tach[illegible]cardia when a diuretic is added to captopril [illegible] be harmful in some patients with a compromise[illegible] cardiovascular system and requires caref[illegible] con[illegible]sideration before treatment Addition of low d[illegible] of beta adrenergic blocking agents if not co[illegible]traindicated will control these heart r[illegible] increases The benefits and hazards of long t[illegible] captopril therapy in severe hypertension re[illegible] further assessment

We wish to thank the referring physicians who [illegible] their patients to our care during this protocol, Te[illegible] and Marjorie Thompson for preparation of the ma[illegible] and Mr Mark Karls for careful review of the cas[illegible] forms. We also thank Dr Edward A Jaeger of the De[illegible]ment of Ophthalmology We are grateful to E. R. Sq[illegible] Sons Inc., for supplying us with the drug

REFERENCES

1 Gifford R W., and Tarazi R. C Resistant h[illegible]sion Diagnosis and management, Ann. Intern M[illegible] 88 661 1978
2 Raftos, J The difficult hypertensive Drugs [illegible] 1976
3 Andersson O., Hansson, L. and Sivertsson, R [illegible] hypertension refractory to triple drug trea[illegible] study on central and peripheral hemodynamics. C[illegible]tion 58 615 1978
4 Dustan H P., Tarazi, R C., and Bravo E L. [illegible] dence of arterial pressure on intravascular vol[illegible] treated hypertensive patients. N Engl J Med [illegible] 1972.
5 Finnerty F., Jr Davidov M Mroczek W J [illegible] Gavrilovich, L. Influence of extracellular fluid vol[illegible] on responses to antihypertensive drugs. Circ Res [illegible] 27(Suppl I) I 71 1970

Brunner H R Gavras H Waeber B Kershaw G R Turini, G A. Vukovich R A McKinstry D N and Gavras I Oral angiotensin converting enzyme inhibitor in long term treatment of hypertensive patients Ann Intern. Med **90** 19 1979
Bravo E L. and Tarazi, R C Converting enzyme inhibition with an orally active compound in hypertensive man Hypertension 1 38 1979
Ferguson R K. Turini, G A Brunner H R and Gavras, H A specific orally active inhibitor of angiotensin converting enzyme in man Lancet **1** 775 1979
Swartz S L. Williams G H Hollenberg N K Moore T J and Dlugy R C Converting enzyme inhibition in essential hypertension The hypotensive response does not reflect only reduced angiotensin II formation Hypertension 1 106 1979
Zacest R., Gilmore E and Koch Weser J Treatment of essential hypertension with combined vasodilation and β adrenergic blockade N Engl J Med **286** 617 1972
Sealey J E and Laragh J H How to do a plasma renin assay Cardiovasc Med 2 1079 1977
12 Case D B Atlas S A Laragh J H Sealey J E Sullivan P A., and McKinstry D N Clinical experience with blockade of the renin angiotensin aldosterone system by an oral converting-enzyme inhibitor (SQ 14 225 captopril) in hypertensive patients, Progr Cardiovasc Dis **21** 195 1978
13 Atlas S A Case D B Sealey J E Laragh, J H and McKinstry D N Interruption of the renin angiotensin system in hypertensive patients by captopril induces sustained reduction in aldosterone secretion potassium retention and natriuresis, Hypertension 1 274 1979
14 Hollifield J W., Sherman K. Zwaag R V., and Shand D G Proposed mechanisms of propranolol s antihypertensive effect in essential hypertension N Engl. J Med **295** 68 1976
15 Prins E J L. Hoorntje S J Weening J J and Donker A J M Nephrotic syndrome in patient on captopril, Lancet **2** 306 1979

The role of echocardiography in the selection of mitral valve prosthesis

Charles E Denbow M D
James R Pluth M D
Emilio R Giuliani M D
Rochester Minn

The problem of prosthesis patient mismatch after valve replacement has recently been highlighted with special reference to postoperative problems in patients with small valvular annuli [1]

Previous workers have stressed the occurrence of left ventricular outflow tract obstruction[2, 3] and ventricular arrhythmias after mitral valve replacement with an unduly large prosthesis Some investigators[3] demonstrated a markedly increased operative mortality rate in patients with narrow left ventricular outflow tracts who had received caged ball prostheses as compared to patients with left ventricular outflow tracts of similar dimensions who had received low profile prostheses

This study attempts to analyze the relationships among the mitral valve prosthesis left ventricular outflow tract dimensions and postoperative morbidity and mortality in a relatively large group of patients with pure or predominant mitral valve stenosis

Patients and methods

At the Mayo Clinic between January 1974 and January 1978 140 patients who had preoperative M mode echocardiograms underwent mitral valve replacement for pure or predominant mitral valve stenosis

Seventy of these patients had M mode echocardiograms of sufficient quality to allow accurate measurement of the left ventricular outflow tract dimensions and this group forms the basis of this study There were 56 females and 14 males and their ages ranged from 31 to 72 years the average being 56 years Patients with associated disease of other valves and clinically overt ischemic heart disease were excluded

The preoperative M mode echocardiograms obtained routinely were analyzed by the measurement of the minimum diameter of the left ventricular outflow tract, as indicated by the shortest distance between the anterior mitral leaflet at the beginning of systole and the left side of the interventricular septum [3]

The postoperative in hospital clinical course of each patient was studied by retrospective analysis of case records Low cardiac output syndrome was diagnosed only if the patient exhibited persistent evidence of low systemic arterial blood pressure with signs of reduced peripheral perfusion and oliguria

The surgical techniques employed were similar in all patients with hypothermia and aortic cross clamping being universally utilized

The patients were placed into two main groups group A were those (44 patients) with left ventricular outflow tract diameters in minimal dimension greater than 20 mm (normal dimension) and group B were those (26 patients) with left ventricular outflow tracts less than 20 mm (small dimensions) The mean ages and bypass times of the two groups were comparable (Table I) There were 4 different types of prostheses used (Table II) The low cardiac output syndrome as previously defined and ventricular dysrhythmias occurred in both patient groups (Table III)

From the Division of Cardiovascular Diseases and Internal Medicine and the Section of Thoracic Cardiovascular and General Surgery Mayo Clinic and Mayo Foundation Rochester Minn

Received for publication Oct. 4 1979

Accepted for publication Feb 14 1980

Reprint requests Dr Emilio R. Giuliani Division of Cardiovascular Diseases and Internal Medicine Mayo Clinic 200 First St SW Rochester MN 55901

0002 8703/80/050586 + 03$00.30/0 © 1980 The C. V. Mosby Co.

able I Patients undergoing mitral valve placement

	Group A (44 pts)	*Group B (26 pts)*
/ outflow tract		
diameter (mm)	>20	<20
Range	20 to 30	13 to 19
ean age (yr)	56	56
pass time (min)		
Mean	57	62
Range	31 to 114	31 to 111

able II Types of prostheses used for patients ndergoing mitral valve replacement

Prosthesis	*Group A*	*Group B*	*Total*
arr Edwards	13	13	26
ork Shiley	11	4	15
ncock	14	9	23
aunwald-Cutter	6	0	6
Total	44	26	70

Three categories were evaluated patients with rmal (> 20 mm) and narrow (< 20 mm) left ntricular outflow tracts who had received ball d cage prostheses (Starr Edwards) and pa ents with narrow outflow tracts who had ceived low profile prostheses (Bjork Shiley) Table IV)

esults and discussion

The overall operative mortality rate for the tients in this study (three of 70 4%) was gnificantly lower than that observed in a pre ous report[5] Since the patients in the latter port were operated on approximately 5 years fore the present patient group this difference ay reflect significant improvements in anesthet and surgical techniques that have occurred ring this period

The incidence of the low cardiac output syn ome was not significantly different in the tients with normal sized outflow tracts as com red to those with narrow outflow tracts or in e patients who received Starr Edwards pros eses in these two patient groups

Thus we could find no evidence of an increased cidence of low cardiac output in patients with nall outflow tracts who received ball and cage ostheses as has previously been noted[2,3,6]

Table III Postoperative complications in patients undergoing mitral valve replacement

Complication	*Group A (44 pts)*	*Group B (26 pts)*
Ventricular dysrhythmia	8 (18%)	4 (15%)
Starr Edwards	5	2
Braunwald Cutter	2	0
Hancock	1	1
Bjork Shiley	0	1
Operative mortality	1 (2%)	2 (8%)
Low output syndrome	7 (16%)	6 (23%)
Bjork Shiley	2	1
Hancock	3	4
Braunwald Cutter	1	0
Starr Edwards	1	1
Mean cardiac index (L/min/M)	1 4	1 7
Mean bypass time (min)	58	75

Table IV Patients undergoing mitral valve replacement

	Group A	*Group B*	
	Starr Edwards (13 pts)	*Starr Edwards (13 pts)*	*Bjork Shiley (4 pts)*
Bypass time (min)	46	55	71
Low output syndrome	1 (7%)	1 (7%)	1 (25%)
Ventricular dysrhythmias	5 (38%)	2 (15%)	1 (25%)
Operative mortality	0 (0%)	0 (0%)	1 (25%)

Only four patients with narrow outflow tracts received low profile prostheses (one patient developed a low cardiac output syndrome) Thus because of the few patients involved this study does not allow a satisfactory answer to the question of whether the use of a low profile prosthesis would reduce the incidence of the low cardiac output syndrome

Ventricular dysrhythmias were more frequent in the group of patients receiving ball and cage prostheses who had normal sized outflow tracts as compared with those who had narrow outflow tracts This finding suggests that in these patients the possibility of mechanical irritation of the left ventricular myocardium producing

ventricular irritability was not a factor because this effect would be more likely to occur in patients with narrow outflow tracts In this respect other mechanisms that contribute to ventricular ectopy such as hypoxemia hypokalemia acid base disturbances and mechanical stimulation by intracardiac lines[7] need to be considered

Patients with normal and narrow outflow tracts who received Starr Edwards prostheses underwent similar surgical techniques (all had hypothermia and aortic cross clamping) and all had similar durations of bypass

No patient receiving a Starr Edwards prostheses died and thus we could not demonstrate any increased operative mortality in the group with narrow outflow tract who had received ball and-cage prostheses—a finding that is distinctly different from that of previous studies[5]

Summary

Assessment of the left ventricular outflow tract was made echographically in 70 patients who subsequently received a mitral prosthesis Group A (44 patients) had normal left ventricular out flow tract width (> 20 mm) 13 received the Starr Edwards prosthesis and nine received the Braunwald Cutter prosthesis There were two patients with low cardiac output syndrome and no hospital deaths Group B (26 patients) had a narrow left ventricular outflow tract (< 20 [illegible] Thirteen patients received the Starr Edw[illegible] prosthesis. One patient had low cardiac out[illegible] syndrome and there were no hospital deaths. W[illegible] conclude that the use of the ball and-cage pro[illegible] thesis in the mitral position in patients wi[illegible] narrowed left ventricular outflow tract (< [illegible] mm) measured echographically is not associa[illegible] with an increased surgical risk

REFERENCES

1 Rahimtoola S H The problem of valve prosthes[illegible] patient mismatch, Circulation 58 20, 1978.
2. Hughes, R. K. Complications of Starr Edwards [illegible] valve replacement J Thorac Cardiovasc Surg 49 [illegible] 1965
3. Lillehei, R. C., Dietzman R. H and Bloch, J E. Hypotension and low output syndrome following card[illegible] pulmonary bypass, in Norman J C., editor Cardi[illegible] surgery New York 1967 Appleton-Century-Cro[illegible] p 438
4 Reid J A., Bricker D L., Alexander J K and De[illegible] key M E A late complication of caged ball mitral valve prosthesis left ventricular incorporation of cage diagno[illegible] sis and surgical correction Am. J Cardiol. 28 [illegible] 1971
5. Nanda N C Gramiak R., Shah, P M DeWeese J A and Mahoney E B Echocardiographic assessment of left ventricular outflow width in the selection of mitral valve prosthesis, Circulation 48 1208, 1973.
6. Cooley D A Bloodwell, R. D., and Hallman, G. L. Mitral valve replacement with a discoid prosthesis, [illegible] Thorac Surg 3 487 1967
7 Humphries, J O Gott, V L., and Benson, D W Care of the patient undergoing valvular heart surgery Pr[illegible] Cardiovasc Dis. 15 449 1973.

omparison of antiarrhythmic effects of oral rajmalium bitartrate and intravenous lidocaine acute myocardial infarction

ulf Dirk Bussmann M D
ybille Schreiber
artin Kaltenbach M D
ankfurt West Germany

ntravenous lidocaine is widely used in the treat ent of ventricular arrhythmias in acute myocar al infarction[1-9] Some authors favor its pro hylactic use in all patients with myocardial farction[6,9-12] Prajmalium bitartrate is the salt the quartary ajmalium base isolated from auwolfia serpentina and has potent antiar ythmic effects The refractory period is creased and the conduction velocity is reduced is evident from an increased AH and HV tervals[8]

Numerous studies document the antiarrhyth ic effect of prajmalium bitartrate in patients ith persistent ventricular arrhythmias[13 2] An fect was also proved in patients with acute yocardial infarction compared to an untreated ntrol group[3 1]

Administration of intravenous drugs is pre rred in the treatment of arrhythmias in acute yocardial infarction In the present study the fect of intravenously administered lidocaine d of orally administered prajmalium bitartrate as compared The onset of effect of both drugs d their efficacy in the reduction of premature ntricular complexes and of runs of these com exes were quantitatively compared to the sults in an untreated control group

om th Department of Cardiol gy Center of Int rn l Medicin i rsity Clinic of F nkfurt/M West G rmany

ce ed f public tion Feb 1 1979
epted f publi ti n J n 4 19 9

print requests Prof Dr M d W D Bussm nn Zentrum d eren Medizin Abteil ng fur Kardi logie Klinikum d Uni ersitat kfurt Theodor St rn Kai 7 6000 F ankfurt a M 0 West G rma

Patients and methods

Thirty five patients with myocardial infarction were studied The spontaneous frequency of pre mature ventricular contractions was registered during a 4 to 6 hour control period in which 7 to 250 ectopic beats per hour were counted Patients with life threatening frequencies of premature ventricular contractions and runs of these com plexes were not included in the protocol These patients were immediately given lidocaine intra venously The remaining patients were divided at random in control and treatment groups In nine patients prajmalium bitartrate (Neo Gilurytmal Giulini Pharma Hannover West Germany) was administered orally and compared randomly to control patients Then nine patients received lidocaine (Xylocaine Astra Chemicals GmbH Wedel/Holstein West Germany) intravenously and were compared randomly to untreated patients Thus a total of 17 patients had no antiarrhythmic therapy

The patients of the control group had a mean age of 58 years Nine of 17 patients had inferior and seven had anterior myocardial infarction In one patient the area of infarction could not be localized The infarction assessed according to the onset of pain occurred an average of 3 5 hours prior to the beginning of the control period Patients treated with prajmalium bitartrate had a mean age of 60 years three of these patients had anterior and six had inferior myocardial infarc tion Infarction occurred in the mean 5 7 hours prior to the control period Patients treated with lidocaine (n = nine) had a mean age of 54 years four of these patients had anterior and five had

0? 8 03/80/0.0589 + 09$00 90/0 © 1980 The C V Mosby Co

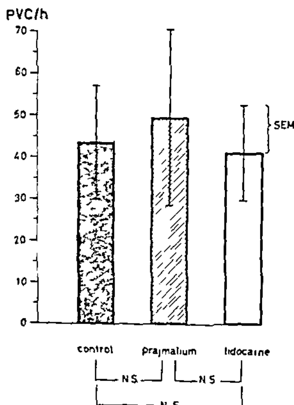


Fig 1 All patients received no antiarrhythmic treatment during a 4 to 6 hour control period The frequency per hour of premature ventricular complexes *(PVC/h)* did not differ significantly NS = not significant

inferior myocardial infarction which occurred at the average 31 hours prior to the control period

Registration of arrhythmias Premature ventricular contractions and runs of such complexes—defined as two to nine ventricular beats—were quantified from stored continuous electrocardiographic tape recordings (Meditape AR Siemens AG Erlangen W Germany) using a semiautomated arrhythmia detection system This device registers all ectopic beats missed beats and all artifacts All events are inscribed on a strip chart recorder together with the last two to three normal QRS complexes which are stored by a special device The recordings were analyzed by hand every hour or every other hour The heart rate and the frequency of arrhythmias detected with an incorporated automatic analyzer were monitored by a trend recorder

Protocol After the control period nine patients received prajmalium bitartrate in three single doses at 4 hour intervals (total dose 60 mg) with a subsequent drug free period of 18 hours The total investigation period lasted 32 hours

After the control period nine other patients received permanent infusions of lidocaine By means of an infusion pump (Perfusor Braun West Germany) patients received 2 1 mg/min corresponding to a total dose of 3000 mg in hours The total investigation period lasted hours Only in three patients was an initial bolus injection (100 mg intravenously in 3 minutes) of lidocaine administered These three patients had premature ventricular contractions and numerous runs of such complexes which required an immediate bolus injection

Frequency of premature ventricular contractions per hour and of runs of such complexes per hour were compared in all groups during antiarrhythmic treatment The percent frequency was compared with that in the control period Statistical analysis was done using Student s t test for unpaired comparison with a two tailed error probability (2 p)

Results

Comparability of patient groups The initial 4 to 6 hour control period prior to onset of treatment was necessary to establish comparable values in all three groups In the control group 43 ± 14 (mean ± 1 standard deviation) premature ventricular complexes (PVC) per hour occurred Patients treated with lidocaine had 41 ± 11 PVC/hr and those treated with prajmalium bitartrate had 49 ± 21 PVC/hr Frequencies did not differ significantly (Fig 1 and Table I) Only initial values of runs of premature ventricular complexes differed however insignificantly (control group 2 2 lidocaine group 5 1 prajmalium bitartrate group 6 9 runs/hr)

Patients in all groups had similar enzyme values (GOT CK and LDH) Peak creatine kinase values were similar in all three groups indicating a comparable extent of infarcted area Serum potassium values were comparable in the control and in the lidocaine group Only patients of the prajmalium bitartrate group had lower potassium values (Fig 2)

Premature ventricular complexes The frequency of premature ventricular complexes decreased under both drugs and also in the control group Six hours after the administration of

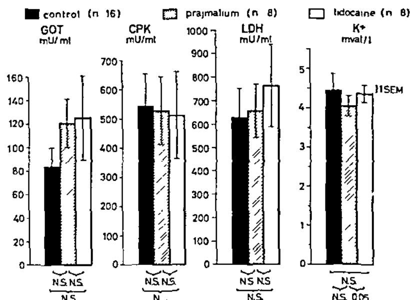


Fig 2 The mean peak enzyme values of GOT CPK LDH and serum potassium are shown for all three groups. Enzyme values especially creatine kinase values did not differ significantly indicating comparable infarct sizes. Serum potassium values were lower in the prajmalium group than in the lidocaine group

able I Absolute values of premature ventricular complexes per hour (PVC/hr) in the control roup and in both treated groups during control period and in the following hours (hr) values epresent mean ± standard error of the mean (SEM)

	Control period	*? hr*	*4 hr*	*6 hr*	*8 hr*	*10 hr*	*12 hr*	*14 hr*	*16 hr*	*18 hr*	*20 hr*	*22 hr*	*24 hr*	*26 hr*
ontrol group (n = 1/)	43 4 ±13 5	45 5 ±18 5	43 2 ±15 ?	34 2 ±10 2	30 6 ±8 6	30 7 ±9 6	?7 7 ±10 8	23 6 ±8 8	18 6 ±6 4	20 ±6 8	20 7 ±7	18 6 ±8	19 9 ±8 5	18 8 ±8 2
rajmalium bi tartrate (n = 9)	49 2 ±20 9	39 ±16 4	39 6 ±23 4	13 ±5 5	3 5 ±0 9	1 7 +0 8	2 3 ±1 4	1.8 ±0 8	2 6 ±1 4	2 0 8	1.3 ±0 7	3 1 ±2 3	3 ±1 8	4.9 ±?7
idocaine (n = 9)	40 8 ±11 4	40 8 ±2? 3	33 6 ±21 8	26 ±18 7	10 6 ±5 8	5 3 ±2 1	4 ±1 5	3 4 ±1.2	3 3 ±1 4	6.2 ±5 1	4.5 ±3 5	1 1 ±0 4	1 ±0 6	0 6 ±0.2
ontrol vs prajmalium 2 P	n s	n s	n.s	<0 10	<0 025	<0 025	<0 10	<0 05	<0 05	<0 05	<0 05	<0 10	<0 10	n.s.
ontrol vs lido-caine 2 P	n s	n.s	n.s	n s	<0 10	<0 05	<0 10	<0 10	<0 05	<0 10	<0 10	<0 10	<0 10	<0 10
rajmalium vs lido caine 2 P	n s	n.s	n s	n.s	n.s	<0 10	n.s	n.s	n.s	n.s	n.s	n.s	n.s	n.s

s = not signific nt n = number of pat ents

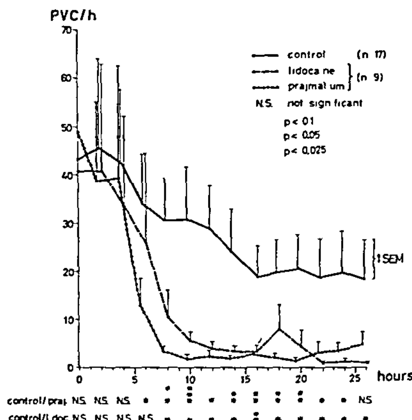


Fig 3 Frequency of premature ventricular complexes per hour *(PVC/h)* during the total investigation period. There was a mild increase and subsequent slow decrease of ectopic beats in the control group With both medications, lidocaine and prajmalium bitartrate there was a marked decrease in premature ventricular complexes. A significant difference was found in the control group after 6 hours under prajmalium bitartrate and after 8 hours under lidocaine administration Mean ±1 standard error of the mean *(SEM)*

prajmalium bitartrate the frequency of premature ventricular complexes was reduced to 13 PVC/hr as compared to 34 PVC/hr in the control group Eight hours after onset of therapy patients treated with lidocaine had 11 PVC/hr compared to 31 PVC/hr in the control group Ten hours after onset of therapy the frequency of premature ventricular complexes was reduced to 1 7 PVC/hr under prajmalium and to 5 3 PVC/hr under lidocaine while patients of the control group had 31 PVC/hr (Fig 3 and Table II)

In all patients the frequency of premature ventricular complexes per hour during the control period prior to medication was listed as 100% (Fig 4 and Table II) While in control patients premature ventricular complexes increased an immediate reduction was registered in the prajmalium and in the lidocaine group A significant difference however was noted only 6 hours after the onset of therapy After 8 to 10 hours with medication the peak drug effect was reached when premature ventricular complexes were reduced to 6% under prajmalium and to 20% under lidocaine administration PVCs in the control group amounted to 180%

The frequency of premature ventricular complexes was only once (10th hour) significantly lower under prajmalium bitartrate compared to lidocaine administration In general there was no significant difference in the drug effect of both medications

Runs of premature ventricular complexes Runs of premature ventricular complexes increased markedly in the control group especially during the first 4 hours (285%) Thereafter runs decreased spontaneously to varying degrees Under lidocaine runs also increased initially but were clearly reduced thereafter Although runs of premature ventricular complexes occurred less frequently under lidocaine than in the control group there was no significant difference between groups (Fig 5 and Table III)

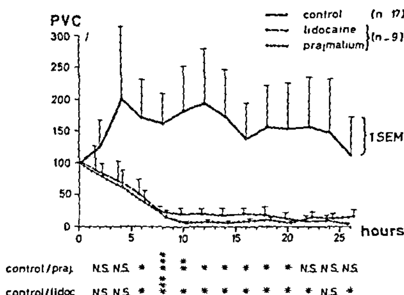


Fig 4 Frequency of premature ventricular complexes during the control period is listed as 100 percent In the control group premature ventricular complexes further increased, whereas in both treatment groups ectopic beats were immediately reduced After the sixth hour a significant difference was seen in the control group Prajmalium bitartrate s effects appear earlier and are more pronounced than the effects of lidocaine

II Frequency of premature ventricular complexes in percent (PVC in %) of the control period ι the control group and in both treated groups values represent mean ± standard error of the an (SEM)

	Control period	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr	14 hr	16 hr	18 hr	20 hr	22 hr	24 hr	26 hr
ontrol group (n = 17)	100	124 ±41	200 ±107	169 ±47	180 ±70	19? ±86	171 ±74	137 ±16	154 ±64	153 ±72	154 ±78	145 ±84	111 ±60	
ıum bı tar trate (n = 9)	100	84 ±18	67 ±25	37 ±19	14 ±7	5 ±2	6 ±2	5 ±2	8 ±3	9 ±4	4 ±2	13 ±9	11 ±7	14 ±10
locaine (n = 9)	100	87 ±32	71 ±30	51 ±23	25 ±7	20 ±9	20 ±12	18 ±9	20 ±12	18 ±13	13 ±8	9 ±6	10 ±8	4 ±2
ontrol vs praj mal ıum 2 P	n.s	n.s	<0 1	<0 025	<0 05	<0 1	<0 1	<0 1	<0 1	<0 1	n.s.	n.s.	n.s	
ontrol vs. lido caine 2 P	n.s.	n.s	<0 1	<0 0?5	<0 1	<0 1	<0 1	<0 1	<0 1	<0 1	<0 1	n.s.	<0 1	
ajmal ıum vs lido- caine 2 P	n.s	n.s	n.s	n.s	0 1	n.s	n.s	n.s.	n.s	n.s	n.s.	n.s.	n.s	

ι.s. = not signifi nt n = number of patients hr = hrs

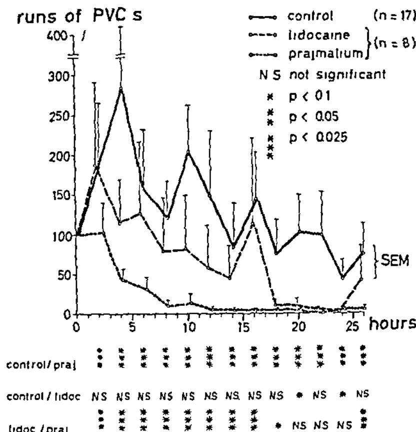


Fig 5 This figure illustrates the frequency of runs of premature ventricular complexes in percent of the control period There was a significant increase (285 percent) in the control group within the first 4 hours, with a subsequent intermittent decrease Under lidocaine administration there was an initial increase and thereafter a marked reduction The difference to the control group was not significant Under prajmalium bitartrate administration there was no initial increase Subsequently an effective and significant reduction of runs of premature ventricular complexes was manifested

Under prajmalium bitartrate runs of premature ventricular complexes did not increase Runs were quickly and effectively reduced to between 4 and 1% in the twelfth hour There was a significant difference to the control group after 2 hours with medication It should be noted that runs of such complexes were also significantly reduced when compared to the lidocaine group (Fig 5 and Table III)

Discussion

It is particularly difficult to study the efficacy of antiarrhythmic drugs in the acute stage of myocardial infarction The individual frequency of premature ventricular complexes varies largely from patient to patient Following infarction an initial increase in ectopy is followed by a moderate spontaneous decrease Therefore a control group with no antiarrhythmic medication is needed in any such study Furthermore patient groups should be statistically comparable with regard to time elapsed between infarction and onset of therapy infarct localization mean age infarct size (CK values) and potassium values

The present findings document similar drug effects of both oral prajmalium bitartrate and intravenous lidocaine in the reduction of premature ventricular complexes in acute myocardial infarction Therapeutic doses of both drugs were given i e 20 mg prajmalium bitartrate orally every 4 hours and 2 1 mg /minute lidocaine intravenously Prajmalium bitartrate seems to have a more pronounced peak effect In three of the patients who received an initial bolus injection of 100 mg of lidocaine premature ventricular complexes were not more rapidly reduced than in the remaining six patients

In general antiarrhythmic drug effects seem to be limited during the early phase of acute myocardial infarction In both treated groups premature ventricular complexes were reduced slowly In the control group premature ventricular com

III Runs of premature ventricular complexes in the control group and in both treated groups quency of runs during control period is listed as 100 percent—time elapsed since beginning of hr = hours (values represent mean ± standard error of the mean [SEM])

		Control period	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr	14 hr	16 hr	18 hr	20 hr	22 hr	24 hr	26 hr
roup	(n = 17)	100	192 ±74	285 ±128	159 ±73	119 ±47	204 ±58	149 ±72	84 ±55	144 ±60	75 ±43	104 ±46	100 ±54	43 ±21	75 ±39
jmal um bi tar	(n = 8)	100	101 ±35	42 ±14	30 ±14	8 ±8	12 ±8	4 ±4	3 ±3	1 ±1	1 ±1	1 ±1	0 ±0	1 ±1	1 ±1
o- ine	(n = 8)	100	188 ±105	115 ±53	127 ±90	79 ±68	82 ±68	58 ±57	42 ±42	113 ±109	8 ±8	7 ±7	1 ±1	0 ±0	42 ±42
ntrol vs 4) nal ium	2 P		<0 005	<0 0005		<0 0005		<0 0005		<0 0005		<0 0005		<0 0005	
ntrol vs) caine	2 P		n.s	n.s	n.s	n.s	n.s.	n.s.	n.s	n.s	n.s	<0 1	n.s	<0 1	n.s
mal ium vs ido caine	2 P		<0 0005	<0 0005		<0 0005		<0 0005		<0 0005	<0 1	n.s	n.s	n.s	<0 0005

= not significant n = number of patients.

exes and runs of such complexes still increased this stage

Runs of premature ventricular complexes were effectively reduced under prajmalium bitar ate There was however no significant effect on frequency of such runs in the lidocaine group arently runs of premature ventricular com exes were more effectively reduced under praj alium bitartrate than under lidocaine Howev this may be due to the relatively low dose of ocaine used

Prajmalium bitartrate During the first two urs after the onset of therapy prajmalium itartrate reduced premature ventricular com xes by 16% Wette and Nieth [2] reported on the of drug effect after one hour The duration the drug effect lasted 5 to 6 hours The wn side effects of the drug are QRS enlarge it at higher doses and cholestasis during ic application in rare cases [2] In this udy it should be noted that QRS complexes did enlarge and heart failure was not aggra ated

Various long term studies confirmed the effect of prajmalium bitartrate [2, 13, 16, 7, 19, 21, 27] In these papers a considerable low rate of side effects such as gastrointestinal disorders QRS widening and intrahepatic cholestasis have been reported [2, 1, 19] 21 22 25 Administration of more than 3 mg/kg body weight caused intoxica tion

Lidocaine Lidocaine remains the standard drug in the treatment of acute myocardial infarc tion Bearing in mind the spontaneous increase in the frequency of ectopic beats in the control group it cannot be assumed that compared to oral medication lidocaine reduces premature ven tricular contractions abruptly to zero even if an initial bolus had been administered in every patient

Many authors favor the administration of an initial bolus injection of lidocaine [4, 5, 6, 8] We comply with this recommendation only in part and favor a bolus injection only in patients with a high rate of ventricular ectopic beats Further more in the presence of intraventricular conduc tion disturbances or multiple arrhythmias a slow onset of therapy seems advisable as is evident

from the literature [30] Side effects have frequently been reported after bolus injections [4,?] [3,3] According to Borer and associates [3] a bolus injection with a subsequent permanent infusion does not favorably affect fibrillation threshold Considering that it takes 6 to 8 hours before the full drug effect is reached a bolus injection with a half life of 20 minutes cannot have a major premanent effect [9,3]

In only three of the nine treated patients was a bolus injection of 100 mg of lidocaine necessary in this study because of frequent ventricular ectopic beats In these three patients the reduction of premature ventricular complexes was not more rapid than in those patients not given a bolus injection In general however one or two bolus injections have to be recommended to reach therapeutic blood levels of lidocaine in an appropriate time period

In the literature recommendations for the prophylactic use of antiarrhythmic drugs in patients with acute myocardial infarction are contradictory to date Lie and colleagues[11] reported a significant decrease in the frequency of ventricular fibrillation in patients with acute myocardial infarction who initially received a bolus injection of 100 mg and subsequently 3 mg/minute of Lidocaine over a period of 48 hours Mogensen and co-workers had similar results Bleifeld and associates however found no difference in the frequency of premature ventricular complexes after the prophylactic administration of lidocaine as compared to an untreated control group Ramdohr and Wirtzfeld and colleagues concluded that in general lidocaine should not be administered to prevent rhythm disturbances Manifest disturbances however should be treated adequately and effectively

Proper dosage of lidocaine was studied by Bleifeld and associates Many authors recommend administration of the dose used in this study

According to Simon only excessively high doses of more than 750 mg/kg body weight may cause major side effects In the literature drowsiness convulsions parasthesias rhythm and intraventricular conduction disturbances and atrioventricular blocks have been reported [20] following a bolus injection and infusion of lidocaine in the dosage range between 2 and 4 mg/minute

In conclusion a similar beneficial effect on the frequency of premature ventricular comple acute myocardial infarction was found afte oral administration of prajmalium bitartrat after the intravenous administration of lido as compared to an untreated control group I doses used oral prajmalium bitartrate bec effective as early as does intravenous lido However a bolus injection of lidocain was in only three of the nine treated patients. malium bitartrate also significantly reduces of premature ventricular complexes Side e were not observed either under lidocaine or t prajmalium bitartrate treatment Therefore initial phase of myocardial infarction may al effectively treated with prajmalium bitartr

Summary

In 35 patients with acute myocardial infar premature ventricular complexes were quan from stored continuous electrocardiographic recordings using a semiautomated arrhyt detection system Seventeen patients sepa at random received no antiarrhythmic drug formed the control group In nine patients malium bitartrate was given orally at a dose mg (20 mg every 4 hours) Nine patients permanent infusions of 2 1 mg/minute lido (corresponding to a daily dose of 3 g) In treated groups premature ventricular comp decreased significantly as compared to the taneous frequency in the control group Six h after the onset of therapy premature ventri complexes were reduced to 37% of the initial in the prajmalium bitartrate group and to 3 the lidocaine group whereas in the control g frequency increased (169%) The peak effect reached after ten hours when premature ver ular complexes were reduced to 5% under malium bitartrate and to 20% under lido administration

Runs of premature ventricular complexes nearly completely suppressed after admini tion of prajmalium bitartrate Under lido administration runs were moderately and significantly reduced Eight hours after the of therapy runs were reduced to 8% of the value under prajmalium bitartrate and to 79% under lidocaine The effect of prajma bitartrate on runs of premature ventricular c plexes was significantly more pronounced t the effect of lidocaine

The present study documents that

administered prajmalium bitartrate is an alternative to intravenous administration of lidocaine in the treatment of ventricular arrhythmias after acute myocardial infarction

REFERENCES

1. Coltart D J Berndt T B Kernoff R, and Harrison D C Anti arrhythmic and circulatory effects of Astra W 3609—a new lidocaine like agent Am J Cardiol 34 35 1974
2. Dransfeld B Zur Behandlung der ventrikularen Extrasystolie mit N n Propyl Ajmalinium hydrogencarbonat (NPAB) Therapiewoche 21 3637 1971
3. Gadermann F Der Herzanfall durch Storungen der Reizbildung und Erregungsleitung Internist 12 39 1971
4. Harrison, D C Practical guidelines for the use of lidocaine JAMA 233 1202 1975
5. Maurer W Soforttherapie tachykarder Rhythmusstorungen Rhein Aztebl. 27 825 1973
6. Ramdohr B Rhythmusstorungen bei akutem Myokardinfarkt Diagnostik und Behandlung *in* Antiarrhythmika Prager Symposium 1973 Haviar V ed Vydavatelstvo Dsveta Martin/CSSR 1974
7. Runge M Augustin H J and Dorner V Zentralnervose Erscheinungen bei Xylocain Intoxikation Archiv Toxikologie 28 72 1971
8. Schroder R Buschmann H J Dennert J Ramdohr B and Schuren K P Sofortmassnahmen beim Herzinfarkt Med Welt 20 701 1969
9. Wirtzfeld A Himmler F C and Baedeker W 1 1–Uberleitung bei Vorhofflattern durch Lidocain Z Kardiol 62 887 1973
10. Bleifeld W Merx W Heinrich, K W and Effert S Lidocain zur Arrhythmieprophylaxe beim frischen Infarkt Verh.Dtsch Ges Inn Med 78 101 1972
11. Lie K I Wellens, H J Van Capelle F J and Durrer D Lidocaine in the prevention of primary ventricular fibrillation A double blind randomized study of 212 consecutive patients N Engl J Med 291 13 4 19 4
12. Mogensen L Prophylactic use of lidocaine in a coronary care unit *in* Symposium on Cardiac Arrhythmias in Elsinore/Denmark Sande E Flensted-Jensen E and Olesen K H eds Sodertalje/Sweden 1970 AB Astra p 69 710
13. Bussmann W D Hanel H J and Kaltenbach M Die Wirkung von Ajmalin bitartrat auf die ventrikulare Extrasystolie beim frischen Herzinfarkt Dtsch Med Wschr 99 2443 19 4
14. Bussmann W D Muller E and Kaltenbach M Wirkung von Prajmalium bitartrat auf die ventrikulare Dauerextrasystolie im Vergleich mit Procainamid Dtsch Med Wschr 101 278 1976
15. Bussmann W D Muller E Hanel H J and Kaltenbach M Orally administered prajmalium bitartrate in acute and chronic ventricular arrhythmias Am J Cardiol 41 577 1978
16. Koch R Klinische und experimentelle Untersuchungen uber Wirkung und Wirkdauer von NPAB bei Herzrhythmusstorungen Arzneim Forsch 22 20 9 19 2
17. Rosenkranz K A, and Schroder W H Ergebnisse der oralen Therapie von Herzrhythmusstorungen mit N n Propyl Ajmalinium Bitartrat Herz/Kreisl 1 4 1969
18. Seipel L Both A Breithardt G, Gleichmann U, and Loogen F Action of antiarrhythmic drugs on His bundle electrogram and sinus node function Acta Cardiologica 18 251 1974
19. Schoenberg A Samuel, A Freidmann J, and Sklerovski, S Ajmaline bitartrat in arrhythmias Harefuah—J Isr Med Assoc 86 70 1974
20. Simon H Herzwirksame Pharmaka Munich, Berlin Vienna 19 4 Verlag Urban & Schwarzenberg
21. Wegehaupt R, and Hager W Behandlung von Herzrhythmusstorungen mit N n Propyl Ajmalin Bitartrat Dtsch Med Wschr 95 938 1970
22. Wette K and Nieth, H Beitrag zur Behandlung von Herzrhythmustorungen mit N Prophyl ajmalinium hydrogentartrat Therapiewoche 24 3736 1974
23. Bleifeld W, Merx, W, and Effert S Klinische Pharmakologie und Nebenwirkungen einiger Antiarrhythmika Dtsch Med Wschr 96 671 1971
24. Homburger H and Antoni H Elektrophysiologische Effekte von N n Ajmalinium hydrogencarbonat (NPAB) am isolierten Saugetiermyokard *in* Herzrhythmusstorungen Second Vienna Symposium Antoni, H and Effert S eds, Stuttgart New York, 1974 Schattauer Verlag p 180-195
25. Klein W W, Pavek, P and Brandt D Verhalten der linksventrikularen Dynamik unter NPAB Arzneim Forsch. 24 2048 1974
26. Weidner A and von Philipsborn, G Vergleichende experimentelle Untersuchungen uber Intoxikationen mit Ajmalin und N n Propyl ajmalinium hydrogentartrat (NPAB) Arzneim Forsch. 21 685 1971
27. Johannes E and Kugler G Die Beeinflussbarkeit myokardialer Heterotopien durch Ajmalinbitartrat Med Welt 23 651 1972
28. Harrison D C Stenson R E and Constantino R T The relationship between blood levels, infusion rates and metabolism of lidocaine to its antiarrhythmic action *in* Symposium on Cardiac Arrhythmias in Elsinore/Denmark, Sandoe E Flensted-Jensen E and Olesen K H eds Sodertalje/Sweden 1970 AB Astra p 427-444
29. Harrison D C and Alderman E L The pharmacology and clinical use of lidocaine as an antiarrhythmic drug Mod. Treatment 9 139 19 2
30. Ross J C and Dunning A J Effects of lidocaine on impulse formation and conduction defects in man Am Heart J 89 686 1975
31. Kaufmann G Lignocaine for arrhythmias, Lancet 1 862 1968
32. Nagle R E, Pilcher J Lignocaine for arrhythmias (Letter to the Editor) Lancet 1 1038 1968
33. Borer J S Harrison L A Kent K M Levy R, Goldstein R E and Epstein S E Beneficial effect of lidocaine on ventricular electrical stability and spontaneous ventricular fibrillation during experimental myocardial infarction Am J Cardiol. 37 860 1976
34. Runge M Lidocain als antiarrhythmische Substanz Med Welt 23 928 1972

The rhythm of the heart in active elderly subjects

A John Camm MB MRCP BSc*
K E Evans MRCS LRCP**
D E Ward MB MRCP, BSc***
Anthony Martin MD****
Crawley West Sussex and London England

The development of ambulatory electrocardiographic monitoring or dynamic electrocardiography (DCG) together with facilities for high speed, semiautomatic playback and analysis has provided a useful investigative tool for the diagnosis of symptoms such as syncope presyncope and palpitations[1-3] The technique has also allowed a more accurate appreciation of the patterns of cardiac rhythm in normal subjects of young and middle age groups[4-8] Previous investigators of older populations who have employed conventional 12 lead electrocardiograms (ECG) have suggested that there is a high incidence of cardiac arrhythmias in this age group[9] and DCG studies of adult populations have revealed an increasing incidence of arrhythmias as age advances[10,11] Rhythm abnormalities are so frequent in hospitalized elderly patients that it has been said that certain arrhythmias should be regarded as a normal finding[12] Other authors have pointed out that there are no adequate data on the rhythm of the normal elderly heart on which to base such a statement This study reports the results of a DCG survey of healthy old people leading active independent lives and defines the spectrum of cardiac rhythms and arrhythmias in group

Patients and methods

A group general practice in Sussex provided a list of all their patients 75 ye and older Of this total of 268 patients 1(who were available fit and consenting f unselected study group Their age distr shown in Table I None of those stu clinical mental disease or any medical requiring acute attention Although all said that they were well insistent direct ing did reveal an incidence of minor pal dizziness and occasional syncope Eigh of the group suffered mild but typica pectoris and 33% had a history of hype Seventy eight percent had no history o vascular disease and 44% had no signific ical history Only 17% were taking no d 61% were not taking any cardioactive tion

This heterogeneous sample compri study group and on each subject a clini tionnaire physical examination and 12 l ing ECG were performed An Avionics tw nel Electrocardiocorder Model 425 was record the electrocardiogram for a sampl of 24 hours The subject was encouraged as near normal a day as possible and to c a diary of the days events and to n symptoms which occurred during the rec

The resting ECG was scrutinized an preted by one observer who had *no know* the results of the 24 hour DCG A trained cian under the supervision of a card

From the Department of Geriatric Medicine Crawley Hospital, Crawley West Sussex England, and the Cardiac Department St Bartholomew's Hospital, London England

Received for publication Feb 13 1979
Accepted for publication Aug 1 1979

Reprint requests Anthony Martin MD Crawley Hospital Crawley West Sussex England

*Lecturer Cardiac Dept St Bartholomew Hospital, London
**Clinical Assistant Dept of Geriatric Medicine Crawley Hospital
***Registrar Cardiac Dept St Bartholomew Hospital London
****Consultant Physician Dept of Geriatric Medicine Crawley Hospital

0002-8703/80/050598 + 06$00.60/0 © 1980 The C. V. M

ulled examples of each arrhythmia which curred during the 24 hour recording In addi visual ectopic counts were made over one te during each 30 minutes of real time and eart rates averaged over a 30 second period ere made each 15 minutes throughout the ording The Avionics scanner Model 660 was d for the analysis

Conventional criteria of rhythm analysis were mployed Ventricular ectopic beats were classi ied according to the scheme outlined in Table II he results in patients aged 75 to 79 years 80 to 4 years and 85 years and over were analyzed ately Subgroups of patients who smoked vere hypertensive or who had evidence of coro y disease were compared with the group as a whole Results obtained from the DCG were ontrasted with those seen on the conventional CG The results in subjects with syncope dizzi ess or palpitations were compared with those who would admit no symptoms

Within 18 months of the start of the study 13 had died and the 24 hour DCG results in is group were considered separately

ts

In 98 cases the dominant cardiac rhythm was inus in origin In this rhythm the heart rate was icted to the range of 50 to 100 beats/minute 73 subjects The heart rate fell below 50 beats/minute in only 11 cases and in seven of ese bradycardia occurred only during sleep In 15 instances the heart rate rose above 100 beats/ e but in no case did the heart rate exceed 130 beats/minute Thirty five tapes revealed sin us rate which did not vary by more than 10 beats/minute throughout the 24 hours The mean eart rate was slightly slower for men (70 beats/ minute) than for women (76 beats/minute) This difference was significant ($p < 0.001$) Sinus arrhythmia defined as adjacent beat to beat P P interval variation of greater than 10% was seen in only 15 of the 98 cases

Established atrial fibrillation was noted in eight cases Only two of these were receiving treatment for control of heart rate and in these two patients who were taking digoxin the heart rate fell intermittently below 40 beats/minute In one other case rapid atrial fibrillation was seen with an averaged heart rate exceeding 150 beats/ minute The remaining five cases had controlled ventricular rates throughout the day of recording

Table I Age distribution—106 subjects

Age (yrs)	Number
75-79	46
80-84	41
85-89	14
90 94	4
> 95	1

and none of these subjects were receiving negative dromotropic drugs There were three examples of paroxysmal atrial fibrillation two detected by ambulatory monitoring and one by conventional 12 lead ECG In these three examples atrial fibrillation produced a rapid ventricular re sponse

Other supraventricular arrhythmias (Table II) occurred in 29 subjects Of these atrial and junctional premature contractions comprised the majority In only one case was paroxysmal atrial tachycardia observed There were two examples of paroxysmal junctional tachycardia Idiojunc tional rhythms were not seen although in four instances junctional escape beats were noted Atrial flutter was not observed

Ventricular arrhythmias were classified accord ing to Lown and Wolf's criteria These criteria were modified for 24 hour ambulatory monitor ing for which there are no clear grading standards presently available An isolated incidence of ven tricular ectopics was defined as less than 10/hour and frequent ventricular ectopics as greater than 100/hour Potentially serious or major ventricu lar arrhythmias (Table II) were seen in 32 sub jects Paroxysmal ventricular tachycardia was present in four cases

In addition to ventricular bradycardia in response to treated atrial fibrillation one case of intermittent complete heart block was discovered on the DCG Otherwise there were no serious bradycardias Sinus node arrest and exit block were not observed However a normal ambulato ry recording which demonstrated sinus rhythm throughout uninterrupted by ectopic beats tachycardia or ventricular pauses was only obtained from 24 patients

The effects of age historical and electrocardio graphic evidence of ischemic heart disease sys temic systolic hypertension and smoking habits were examined separately (Table III) No signifi cant differences in the incidence of normality

Table II The spectrum of cardiac rhythms detected by 24 hour DCG monitoring in 106 subjec

Sinus rhythm		9
	Sinus bradycardia	11
	Sinus tachycardia	15
	Sinus arrhythmia	15
Atrial fibrillation		11
	Established atrial fibrillation	8
	Paroxysmal atrial fibrillation	[illegible]
	Rapid atrial fibrillation	1
	Slow atrial fibrillation	[illegible]
Supraventricular arrhythmias		[illegible]
	Atrial premature beats	2
	Junctional premature beats	[illegible]
	Atrial tachycardia	1
	Junctional tachycardia	[illegible]
	Junctional escape beats	[illegible]
	Atrial flutter	[illegible]
Ventricular arrhythmias		[illegible]
Minor	Isolated ventricular premature beats (< 10/hr)	4
	Moderate ventricular premature beats (10 100/hr)	1
Major	Frequent ventricular premature beats (> 100/hr)	1
	Multiform ventricular premature beats	[illegible]
	Paired ventricular premature beats	[illegible]
	Ventricular bigeminy	[illegible]
	Salvos of ventricular premature beats	[illegible]
	Ventricular tachycardia	[illegible]

supraventricular arrhythmias or major and minor ventricular arrhythmias was found Follow up 18 months after the ambulatory recording revealed that 13 of the 106 subjects had died An analysis of the arrhythmia spectrum of these cases revealed no differences compared with the group as a whole Of the 13 deaths two were sudden and unexplained and both of these subjects had major ventricular arrhythmias in one case ventricular tachycardia at the time of recording

The single 12 lead electrocardiogram taken on the day of ambulatory recording demonstrated entirely normal sinus rhythm in 72 instances Ten recordings demonstrated atrial fibrillation and there were 16 traces demonstrating other supraventricular arrhythmias and 16 examples of major ventricular arrhythmias Comparison with the results of ambulatory monitoring (Table IV) reveal that arrhythmias were detected two to four times more frequently by ambulatory recording than by the conventional 12 lead ECG

Although each patient was encouraged to complete a dairy of daily events and of any symptom suffered during the recording compliance was very poor and direct comparison between symptoms and DCG findings was impossible the occurrence of minor and major arr was compared with the symptoms to subject had admitted in the questionnai V) There was no correlation between dence of these symptoms and the DCG Similar ambulatory recordings were those who did and those who did symptoms

Discussion

It is debatable whether the sample em this study could be regarded as an entire elderly population The frequent occu syncope palpitations dizziness ch hypertension and the high intake of me would suggest that the group is not n criteria which would apply to younger a However insistence on strict normali exclude all but 12 members of the 268 pa years or older cared for by a group practice Instead all the elderly patie this practice who were mentally compe from acute medical complaints and sented to take part in the study were This group probably represents the

able III The distribution of normal and abnormal recordings detected by 24 hour DCG monitoring the whole group and subgroups divided according to age the presence of ischemic heart disease ypertension smoking habits and deaths 18 months following the ambulatory recording

			Normal	*Supraventricular arrhythmias*	*Minor ventricular arrhythmias*	*Major ventricular arrhythmias*
		Total	24 (23%)	29 (27%)	41 (39%)	32 (30%)
	75-79	46	10 (22%)	10 (2?%)	17 (37%)	16 (35%)
	80-84	41	10 (24%)	15 (36%)	16 (39%)	9 (22%)
	> 85	19	4 (21%)	4 (21%)	8 (42%)	7 (37%)
c heart disease	Present	24	6 (25%)	7 (29%)	8 (33%)	7 (29%)
	Absent	82	18 (22%)	22 (27%)	33 (40%)	23 (28%)
	< 160	72	16 (22%)	18 (25%)	29 (40%)	21 (29%)
tolic blood pressure	160 200	31	8 (26%)	10 (32%)	10 (32%)	10 (32%)
	> 200	3	0	0	2 (66%)	1 (33%)
obacco	Non smoker	82	20 (24%)	21 (26%)	33 (40%)	23 (28%)
	Smoker	24	4 (17%)	8 (33%)	8 (33%)	9 (38%)
Deaths	All	13	1 (8%)	6 (46%)	5 (38%)	5 (38%)
	Sudden	2	0	1 (50%)	0	2 (100%)

mbulant population at large more closely than an artificially selected group of strictly ormal subjects

Old people are generally reluctant to cooperate ith studies of this kind which intrude on their rivacy Sixty eight of the 217 people canvassed u our invitation to take part in the study those who did participate some found the ording equipment cumbersome and others ere frightened by the procedure Despite our ncouragement to the contrary these various ors probably modified the participants activ during the day or recording and may have ced the validity of our results These difficul ies could not be avoided but were minimized by ing the recorders and taping the DCG in the ubjects own homes Another technical difficulty ncountered during this study was the inability of his group to accurately complete the diary of ms noted during the day of recording This em is not confined to the older patient [15] but did prevent any direct comparison between symp oms suffered and DCG findings

It is generally accepted that sinus rates decrease linearly with age but in our study sinus bradycardia was uncommon In comparison the ncidence of severe sinus bradycardia in a series of 50 students was 24% Our findings are consis ent with previous studies using the 12 lead ECG or rhythm strips In his review of the surface ECG of patients over 70 years of age Gavey[1] reported only a 2 5% incidence of sinus bradycardia and Kirk and Kvorning[?] noted a lower incidence of sinus bradycardia in patients over 65 years (5 8%) compared with patients below the age of 40 years (9 3%) These authors also contended that sinus bradycardia is seen more frequently in patients with acute medical problems and the relatively low incidence of slow sinus rates in this study may be related to the generally healthy and ambulant nature of the study population

Table IV Comparison of arrhythmias detected by 12 lead ECG and 24 hour DCG

	24 hr DCG	*12 lead ECG*
Normal	24 (23%)	72 (68%)
Atrial fibrillation	10 (9%)	9 (9%)
Supraventricular arrhythmias	29 (27%)	16 (15%)
Minor ventricular arrhythmias	41 (39%)	9 (9%)
Major ventricular arrhythmias	32 (30%)	16 (15%)
Complete heart block	1 (1%)	0

Although sinus arrhythmia was not frequently encountered in this study its incidence is consis tently higher than in previous ECG studies [11] More surprising was the severe restriction in the dynamic range of heart rates in one third of this

Table II The spectrum of cardiac rhythms detected by 24 hour DCG monitoring in 106 subjects

Sinus rhythm		9[illegible] (9[illegible]
Sinus bradycardia		11 (1[illegible]
Sinus tachycardia		13 (1[illegible]
Sinus arrhythmia		15 (1[illegible]
Atrial fibrillation		11 (1[illegible]
Established atrial fibrillation		8 ([illegible]
Paroxysmal atrial fibrillation		3 (3[illegible]
Rapid atrial fibrillation		1 (1[illegible]
Slow atrial fibrillation		2 ([illegible]
Supraventricular arrhythmias		29 ([illegible]
Atrial premature beats		22 ([illegible]
Junctional premature beats		3 (3[illegible]
Atrial tachycardia		1 (1
Junctional tachycardia		2 ([illegible]
Junctional escape beats		4 (4[illegible]
Atrial flutter		0
Ventricular arrhythmias		73 (6[illegible]
Minor	Isolated ventricular premature beats (< 10/hr)	4[illegible] (4[illegible]
	Moderate ventricular premature beats (10 100/hr)	15 (1[illegible]
Major	Frequent ventricular premature beats (> 100/hr)	13 (1[illegible]
	Multiform ventricular premature beats	[illegible]3 (2[illegible]
	Paired ventricular premature beats	4 (4[illegible]
	Ventricular bigeminy	5 (5[illegible]
	Salvos of ventricular premature beats	2 ([illegible]
	Ventricular tachycardia	4 (4[illegible]

supraventricular arrhythmias or major and minor ventricular arrhythmias was found Follow up 18 months after the ambulatory recording revealed that 13 of the 106 subjects had died An analysis of the rhythm a spectrum of these cases revealed no differences compared with the group as a whole Of the 13 deaths two were sudden and unexplained and both of these subjects had major ventricular arrhythmias in one case ventricular tachycardia at the time of recording

The single 12 lead electrocardiogram taken on the day of ambulatory recording demonstrated entirely normal sinus rhythm in 72 instances Ten recordings demonstrated atrial fibrillation and there were 16 traces demonstrating other supraventricular arrhythmias and 16 examples of major ventricular arrhythmias Comparison with the results of ambulatory monitoring (Table IV) reveal that arrhythmias were detected two to four times more frequently by ambulatory recording than by the conventional 12 lead ECG

Although each patient was encouraged to complete a diary of daily events and of any symptom suffered during the recording compliance was very poor and direct comparison between symptoms and DCG findings was impossible How[illegible] the occurrence of minor and major arrhyt[illegible] was compared with the symptoms to whic[illegible] subject had admitted in the questionnaire ([illegible] V) There was no correlation between the [illegible] dence of these symptoms and the DCG fin[illegible] Similar ambulatory recordings were fou[illegible] those who did and those who did not [illegible] symptoms

Discussion

It is debatable whether the sample emplo[illegible] this study could be regarded as an entirely n[illegible] elderly population The frequent occurre[illegible] syncope palpitations, dizziness chest [illegible] hypertension and the high intake of medic[illegible] would suggest that the group is not norm[illegible] criteria which would apply to younger age g[illegible] However insistence on strict normality [illegible] exclude all but 12 members of the 268 patien[illegible] years or older cared for by a group ge[illegible] practice Instead all the elderly patients [illegible] this practice who were mentally competent [illegible] from acute medical complaints and who [illegible] sented to take part in the study were incl[illegible] This group probably represents the el[illegible]

 symptomatic patients The study was per ormed on 106 subjects at home and consisted of a linical questionnaire physical examination rest ng 12 lead ECG and 24 hour taped DCG

Eight subjects had established atrial fibrilla ion (AF) and three had paroxysmal AF Estab shed AF resulted in a rapid ventricular response n one case and a slow ventricular rate in two A ontrolled ventricular response was found in five ubjects who were on no treatment

Of 98 subjects in sinus rhythm 73 had a heart ate of between 50 and 100 beats/minute 11 had inus bradycardia and in only 15 instances did he heart rate intermittently exceed 100 beats/ minute Thirty five subjects had sinus rates that did not vary by more than 10 beats/minute hroughout the 24 hours

The DCG demonstrated isolated ventricular remature beats in 45 subjects and potentially ore serious ventricular arrhythmias in 32 cases entricular bradycardias of any variety were rarely seen Arrhythmias were detected two to four times more frequently by DCG than by 12 lead ECG Within this sample age ischemic heart disease systolic hypertension smoking habits and a history of syncope palpitations or dizziness did not affect the prevalence of any type of arrhythmia

The results of this study demonstrate that although ectopic cardiac rhythms and tachycar dias are common in apparently healthy elderly people ventricular pauses and bradycardias are extremely uncommon

Our thanks are due to Dr Ivan Clout his partners and staff both for their help and for allowing us to investigate patients in their practice

REFERENCES

1 Goldberg A D Raftery E B and Cashman P M M Ambulatory electrocardiographic records in patients with transient cerebral attacks or palpitation Br Med J 4 569 1975

2 Lipski J Cohen L Espinoza J Motro M Dack S and Donoso E Value of Holter monitoring in assessing cardiac arrhythmias in symptomatic patients Am J Cardiol 37 102 1976

3 Wang R Ward D E Camm A J and Spurrell R A J The value of 24 hour ambulatory electrocardiographic recordings in 405 patients with dizziness syncope or palpitations Br Heart J 41 373 1979

4 Southall D P Orrell M J Talbot J F Brinton R J Vulliamy D E Keeton B R Anderson P M and Shinebourne E A Study of cardiac arrhythmias and other forms of conduction abnormality in newborn infants Br Med J 2 597 1977

5 Brodsky M Wu D Denes P Kanakis C and Rosen K M Arrhythmias documented by 24 hour continuous electrocardiographic monitoring in 50 male medical stu dents without apparent heart disease Am J Cardiol 39 390 1977

6 Clarke J M Hamer J Shelton J R Taylor S and Venning G R The rhythm of the normal human heart Lancet ii 508 1976

7 Gavey C J The cardiology of old age Lancet ii 725 1949

8 Mihalick M J and Fisch C Electrocardiographic findings in the aged Am Heart J 87 117 1974

9 Martin A The natural history of atrial fibrillation in the elderly M D Thesis London University 1974

10 Raftery E B and Cashman P M M Long term recording of the electrocardiogram in a normal popula tion Postgrad Med J 52 32 1976

11 Verbaan C J Poole J and Van Wanrooy J Incidence of cardiac arrhythmias in a presumed healthy popula tion Proceedings of the 2nd International Symposium on Ambulatory Monitoring London 1978 Academic Press

12 Gelfand M L The octogenarian electrocardiogram Geriatrics 12 156 1957

13 Burch G E Interesting aspects of geriatric cardiology Am Heart J 89 99 1975

14 Lown B and Wolf M Approaches to sudden death from coronary heart disease Circulation 44 130 1971

15 Camm A J Ward D F and Spurrell R A J Arrhythmias in ambulatory persons Biotelemetry (In press 1979)

16 Landowne M Brandfonbrener M and Shock N W The relation of age to certain measures of performance of the heart and the circulation Circulation 11 567 1955

17 Kirk J E and Kvorning S A Sinus bradycardia A clinical study of 515 consecutive cases Acta Med Scand Suppl 266 625 1952

18 McNamara R J A study of the electrocardiogram in persons over seventy Geriatrics 4 140 1949

19 Dighton D H Sinus bradycardia Autonomic influences and clinical assessment Br Heart J 36 791 1974

20 Agruss N S Rosin E Y Adolf R J and Fowler N O Significance of chronic sinus bradycardia in elderly people Circulation 46 924 1972

21 Wosika P H Feldman E Chesrow E J and Myers G B Unipolar precordial and limb lead electrocardio grams in the aged Geriatrics 5 130 1950

22 Vismara L A Pratt C Price J E, Miller R R Amsterdam E A and Mason D T Correlation of the standard electrocardiogram and continuous ambulatory monitoring in the detection of ventricular arrhythmias in coronary patients J Electrocardiol 10 299 1977

23 Kotler M N Tabatznik B, Mower M M and Tanna ja S Prognostic significance of ventricular ectopic beats with respect to sudden death in the late post infarction period Circulation 47 959 1973

24 Hinkle L E Carver S T and Stevens M The frequency of asymptomatic disturbances of cardiac rhythm and conduction in middle aged men Am J Cardiol 24 629 1969

25 McCarthy S T and Wollner L Cardiac dysrhythmias treatable cause of transient cerebral dysfunction in the elderly Lancet ii 1977

26 Bleifer S B Bleifer D J Hansmann D R Sheppard J J and Karpman H L Diagnosis of occult arrhyth mias by Holter electrocardiography Progr Cardiovasc Dis 16 569 1974

Serum chromium in patients with recent and old myocardial infarction

Abraham S Abraham M D F R C P
Moshe Sonnenblick M D
Maya Eni
Ovadiah Shemesh M D
Ahron P Batt
Jerusalem Israel

Persons dying of coronary heart disease were found to have virtually no chromium in their aortas whereas those dying of accidents or other diseases had aortic chromium [1] Chromium levels in tissues of Americans tended to be low and declined with age [1] whereas tissues of Africans and Orientals contained much higher concentrations Tissues of Thailanders had more chromium than any other group and they also had a very low incidence of aortic atherosclerosis [3]

Chromium deficiency has also been linked with an impairment of glucose tolerance elevated serum cholesterol levels and the causation of aortic plaques in animals

These findings have led to the conclusion that decreased or absent aortic chromium in atherosclerosis reflects the decreased or absent chromium in the coronary arteries and that this condition leads to abnormal metabolism and plaque formation

The measurement of plasma chromium has until recently presented technical difficulties and no information is available regarding the blood levels of chromium in patients suffering from acute myocardial infarction or known to have coronary artery disease

From the Department of Medicine Shaare Zedek Hospital and the Inter Department Equipment Unit Hadassah Medical School, Hebrew University Jerusalem Israel.

Received for publication Feb 28, 1979
Accepted for publication Ju[illegible] 197[illegible]

Reprint requests Dr A S Abraham Dept of Medicine Shaare Zedek Hospital, Jerusalem, Israel

Patients and methods

Forty five patients without serious disea[se] were seen in the outpatient clinics and [h...] volunteers were taken as controls. Diabet[ic sub]jects (fasting blood glucose of over 110 [mg/d]l) were excluded and no patient had a [...] or electrocardiographic evidence of ische[mia,] rheumatic heart disease arteriosclerosis, [hyper]tension or congestive cardiac failure No [...] was receiving medication

Thirty four patients attending the out[patient] clinic who had been hospitalized 6 to 12 [...] previously with proven myocardial inf[arction] were taken as the test group Any patient [with a] fasting blood glucose level of over 110 mg / [...] was also excluded from the study

Thirty seven patients consecutively ad[mitted] with a definite diagnosis of myocardial inf[arction] (that is typical history and electrocardio[graphic] changes together with elevation of serum [...] and LDH) were also studied and the [serum] chromium was determined the morning [after] admission 1 to 4 days later and again 5 to [...] following admission

Finally, the serum chromium was meas[ured in] 14 patients who were either diabetic or wh[o were] receiving intravenous glucose The latte[r were] patients with chest pain who did not ha[ve] electrocardiographic or enzyme changes

Serum chromium was measured by [atomic] absorption spectrophotometry as describ[ed by] Pekarek and associates [4] In each case [blood] samples were taken in polyethylene test [tubes]

 0002-8703/80/0604 + 03$00.30/0 © 1980 The C. V. M[osby Co.]

er an overnight fast and were kept at –20° C
il analysis

There were 32 males and 13 females in the ontrol group and their ages ranged from 22 to 90 ears (mean 49 9 years) The mean serum chro was 1 71 parts per billion (ppb) (S E 0 14)

Thirty four patients (25 males and nine emales) aged 42 to 85 years (mean 59 1 years) ith ischemic heart disease (IHD) all of whom had had a proven myocardial infarct 6 to 12 previously had a mean serum chromium *level of 1 84 ppb (S E ± 0 18)*

Analysis of both groups showed no significant differences due to sex or age nor was there any icant difference between the mean serum hromium levels of the two groups

Serum chromium levels in 37 patients during first 24 hours following a myocardial infarc were not significantly different from our ol population However there was a signifi rise during the next four days to a maximum level of 6 36 ppb (S E ± 0 51 p < 0 001) a subsequent fall to normal levels during the 5 days

The serum chromium in five of these patients between 2 9 and 3 3 ppb that is just below mean plus 2 standard deviations (3 5 ppb) of control group

The serum chromium levels in 22 patients who ere not in cardiac failure was positively corre ated with infarct size as assessed by the maxi rise in SGOT (r = 0 5036 p < 0 05) There no evidence of any relationship between serum chromium levels and the presence or absence of cardiac failure

There was no increase in serum chromium levels in the 14 patients with raised blood glucose levels (diabetic subjects or patients receiving glu cose infusions) nor was there any correlation between blood glucose levels and serum chromi um in the patients with acute myocardial infarc tion

Discussion

The level of serum chromium found in our normal control group compares with recently published data in which a mean of 1 58 ppb (S E ± 0 08) was found in healthy volunteers [7] We found no statistical difference in the mean serum chromium levels between patients known to have IHD and those without any clinical evidence of the disease This by no means excludes *the possibility that the patients in the* control group had pathological coronary (or for that matter any other) arteries however they were symptom free and had no obvious evidence of atherosclerotic disease All our patients came *from Jerusalem and drank the same water and so* presumably had the same intake of chromium However solitary plasma chromium levels are said not to provide a valid index of chromium nutritional status [8] Nevertheless we have been *unable to find evidence of an association between* the serum chromium level and the presence or absence of clinically evident ischemic heart dis ease

Soon after an acute myocardial infarction there is a significant though temporary increase in serum chromium levels This may be due to release from the damaged myocardial tissue as is suggested by the significant correlation with the maximum rise in SGOT However whether the lower concentrations of chromium found in the tissues of patients who have died from their infarct is an acute phenomenon or an accompani ment of their atherosclerotic heart disease is not yet clear

Since all our patients were receiving glucose infusions during the acute stage of their myocar dial infarction and since the infarction itself may lead to a temporary impairment of glucose toler ance the serum chromium levels may have been influenced by changes in the blood glucose [9] Others have indeed reported that an oral glucose challenge results in a temporary increase in plas ma chromium levels However we found no cor relation between serum chromium and blood glucose levels in the 14 patients we examined (with raised blood glucose levels) nor was there any correlation between serum chromium and blood glucose levels in the patients with acute myocardial infarction

Summary

The serum chromium in 45 subjects with no clinical evidence of ischemic heart disease was found to be 1 71 parts per billion (ppb) (S E ± 0 14) In 34 patients with a previously documented myocardial infarction it was 1.84

ppb (S E ± 0 18) The difference was not significant nor was there any difference with age or sex In 37 patients with acute myocardial infarction the serum chromium level rose to a mean of 6 36 ppb (S E ± 0 51 $p < 0\,001$) during the first five days following the infarct returning to normal over the next five days There was no correlation between the serum chromium and blood glucose levels in these patients or in a further 14 patients who were receiving glucose infusions (chest pain without electrocardiographic or enzyme changes) or who were diabetics

We a e grateful to The Joint Research Fund of the Hebrew Un versi y and Hadassah and to the Chief Scientist s Office of the Ministry of Health for their support of this project

REFERENCES

1 Schroeder H A Nason A P., and Tipton I H Chromium deficiency as a factor in atherosclerosis J Chron c Di 23 123 1970
2 Schroeder H A The role of chromium in m nutrition Am J Clin Nutr 21 230 1968
3 Schroeder H A Degenerative cardiovascular the Orient 1 Atherosclerosis J Chronic I 1958
4 Schroeder H A., and Balassa JJ Influence um cadmium and lead on rat aortic lipids and cholesterol, Am J Physiol 209 433, 19
5 Schroeder H A Chromium deficiency in ra drome simulating diabetes mellitus with growth, J Nutr 88 439 1966
6 Schroeder H A The role of trace el ments in cular diseases Med. Clin North Am 58 381
7 Pekarek, R S., Hauer E C., Wannemacher and Beisel W R The direct determination chromium by an atomic absorption spectrop with a heated graphite atomizer Anal Bioche 1974
8 Hambidge K M Chromium nutrition in m Clin Nutr 27 505 1974
9 Glinsman W H Feldman F J and Mertz, W chromium after glucose administration 152 1243 1966

angina after bypass surgery
by early and late arteriography

rt I Hamby M D
Irwin Hoffman M D
I Weisz M D
Julius Garvey M D
George Wisoff M D
New Hyde Park Jamaica and Stony Brook N Y

Aortocoronary bypass surgery has been ac ed[1-5] as an effective therapy in the manage of selected symptomatic patients with docu ed coronary artery disease Although bypass rgery has been followed in some studies by in left ventricular function[6] the le of this surgical treatment in prolonging life mains controversial at present Symptomat and a better quality of life" can anticipated in the majority of patients ergoing successful bypass surgery Recurrent however in the late follow up period not unusual The anatomical basis of recurrent angina pectoris after apparently cessful bypass surgery requires clarification The present report describes the clinical and omical correlates of early and late postoperative angiography in 98 patients evaluated after successful aortocoronary bypass surgery

Material and methods

Between December 1970 and April 1977 a total of 937 patients underwent isolated aortocoronary bypass surgery There were 14 (1 4%) operative deaths Just prior to discharge and after informed consent 570 patients had repeat arteriography to evaluate the patency and morphologic aspects of their coronary bypass surgery This reports describes our experience in 98 of these patients who in their initial postoperative study demonstrated patency of all surgically implanted grafts This initial postoperative study (< 2 weeks) is a routine procedure offered and performed as part of the over all evaluation of patients prior to discharge from the hospital. Each of these 98 patients had a second late follow up arteriographic study (five to 73 months average 2.6 years) after surgery The second angiogram was done either for recurrence of angina pectoris or in patients without symptoms to evaluate the late results of aortocoronary bypass surgery In this asymptomatic group no criteria were used in selection except the willingness of the patient to participate Surgical methods and diagnostic techniques used in these patients have been previously described[18] The study group included 79 men and 19 women with an age range of 33 to 69 years (average 53 years) The clinical information on each patient included data regarding hypertension diabetes mellitus cigarette smoking family history and blood lipids. Cholesterol and triglyceride levels were obtained at the initial study and were considered abnormal when above the 95th percentile for age and sex as defined by Goldstein and co-workers[20] for a control population

A total of 177 grafts (1.8 grafts/patients) including six internal mammary artery grafts, were implanted. Thirty four patients had single grafts, 51 had double grafts 11 had triple grafts and two had quadruple grafts. In order to facili

From the Department of Medicine and Surgery Cardiology and Cardiothoracic Divisions, the Heart Institute of Long Island Jewish-Hillside Medical Center New Hyde Park N Y Queens Hospital Center affiliation, Jamaica N Y and School of Medicine Health Sciences Center State University of New York at Stony Brook, Stony Brook, N Y

Received for publication March 29 1979
Accepted for publication May 1 1979

Reprint requests Robert I Hamby M.D The Heart Institute of Long Island Jewish Hillside Medical Center New Hyde Park, N Y 11040

0002-8703/80/050607 + 0?$00 ?0/0 © 1980 The C V Mosby Co

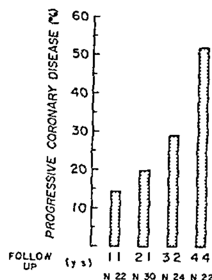


Fig 1 Frequency of progressive coronary artery disease (per cent of patients) as related to the period of follow up The latter period is the time interval between the initial and late postoperative arteriographic study N = number of patients at each interval

tate the postoperative graft visualization study, a metal clip was sutured to the aortic wall at the origin of each saphenous vein bypass Closure was considered present when both selective and aortic root injection failed to visualize the bypass graft In the majority of instances graft closure was accompanied by a dimple in the aortic wall adjacent to the metal clip Incomplete surgical revascularization was considered present if all major coronary arteries with significant occlusive disease could not be grafted In many such instances the diseased vessel was either complete ly blocked without any visible run off demon strated diffuse disease could not be identified at the time of surgery or was considered too small for grafting Progressive coronary disease was considered present if a new area of significant disease was found in the late postoperative study which was either previously normal or only slightly irregular Significant new disease was defined as over 50% narrowing of a coronary artery segment Progressive coronary disease was evaluated in both nongrafted arteries and in grafted arteries distal to the anastomoses Seg ments of the coronaries proximal to grafts were not fully evaluated since in the late arteriograph ic studies the state of these segments could not always be determined Standard statistical meth ods were used to calculate Student s t test for unpaired data and Chi-square analysis for signifi cance

Table I Angiographic correlates on late posto ative evaluation

Recurrent angina pectoris	*Present*	*Absent*	
Number of patients	38	60	
	%	%	Signific
Progressive coronary disease	47	18	p < 0.0
Incomplete surgical revascu larization	37	15	p < 0.0
Graft closure	21	5	p < 0.0
Graft stenosis	5	5	NS
Any one of above factors	92	36	p < 0.0

Results

Of the 98 patients evaluated 38 were referred for recurrent angina pectoris Comparison of these 38 symptomatic patients with the remaining 60 without angina revealed no significant differences in age or incidence of hypertension diabetes mellitus cigarette smoking prior myocardial infarction or abnormal serum lipid levels There was no significant difference in the time interval between early and late postoperative studies in symptomatic or symptom free subjects Recurrence of symptoms occurred between fo and 59 months after surgery (average 2 4 yrs).

Progressive coronary artery disease (Table I) was present in 47% of patients with recurrent angina compared to 18% in asymptomatic patients($p < 0.005$) No particular coronary artery demonstrated any predilection to develop progressive disease In the entire group 29 patients showed significant progression of coronary disease in the late arteriographic study of these 16 (55%) had recurrent angina A completely new, significant coronary artery lesion in the late postoperative arteriographic study was found in 29 (24%) of 121 ungrafted major coronary arteries while in 164 patent grafts the run-off of the native coronary vessel distal to the anastomosis revealed the development of significant new lesions in five instances (3%) In 13 vessels served by completely occluded grafts significant progressive disease was observed in five incl of complete occlusion of the original stenotic segment in two vessels A comparison of the clinical profile in the 29 patients with progressive coronary disease and the remaining 69 patients without new significant lesions is shown in Table II The ages of the patients as well as the incid

le II Clinical profile in patients with and without progressive coronary artery disease

	No progressive disease		Progressive coronary disease present		
Numb r	69		29		Significance
(mean ± 1 S D)	54 ± 8		51 ± 7		
		%		%	
lypertension		40		45	N.S
Diabetes mellitus		12		14	N.S
igarette smoking		57		64	N.S
amily history of					
Coronary artery disease		57		68	N.S
Hypertension		26		27	N.S
Diabetes mellitus		26		32	N.S
holesterol					
Mean ± 1 S D (mgm /dL)	239 ± 37		264 ± 57		p < 0 05
Percent abnormal		8		9	N.S
riglyceride					
Mean ± 1 S D (mgm /dl)	168 ± 79		174 ± 86		N.S
Percent abnormal		23		27	N.S

hypertension diabetes mellitus cigarette oking or elevated serum lipids showed no sig ant difference the mean serum cholesterol /dl) was 264 ± 57 in the group with pro ssive disease compared to 239 ± 37 in those thout progressive disease ($p < 0.05$) Post ative cessation of smoking or decreased lipid levels at late postoperative study did influence the results shown in Table II The idence of progressive coronary artery disease directly related ($p < 0.025$) to the time inter between the early and late postoperative (Fig 1) The average incidence of progres disease was 10 7% of patients per year

Incomplete surgical revascularization (Table I was noted in 37% and 15% of patients respec ively with and without recurrent angina pecto Of these 23 patients with incomplete surgical ascularization 14(61%) were operated during the first 18 months of our experience with coro nary bypass surgery The remaining nine patients underwent surgery during the following five years

Graft closure was present in 21% and 5% respectively of patients with and without angina ($p < 0.025$) All six internal mammary artery grafts to the left anterior descending artery were patent while 13 (7 6%) of 171 saphenous vein grafts demonstrated late closure This represents an average annual attrition rate (average percent saphenous grafts closed/yr) of 3% Nine patients had one graft closed two had two grafts closed and the remaining 87 patients (89%) showed patency of all grafts However in the latter group five patients (two with angina) demonstrated over 50% localized segmental narrowing *(graft stenosis)* of the saphenous vein bypass (Table I) Thus 84% of patients studied angiographically after an average follow up of 2 6 years demon strated all grafts patent and technically satisfac tory—i e no kinks localized stenosis or stenosis at anastomotic site Similarly no angiographic evidence of new significant lesions could be found in 70% of patients during the same follow up period

In 92% of patients with angina pectoris at least one factor (see Table I) was present which could logically explain the presence of recurrent angina compared to 36% in asymptomatic restudied patients ($p < 0.005$) Twenty six patients had only one factor predisposing to recurrent angina These included 14 with progressive coronary dis ease seven were incomplete surgical revasculari zation four with graft closure and one with graft stenosis

Discussion

The beneficial effect of coronary bypass sur gery in the relief of angina pectoris is firmly established Sheldon and associates[1] reported 87% of patients free of symptoms after successful surgical revascularization Schroeder and col

leagues[13] noted that 97 5% of patients undergoing bypass surgery for unstable angina were either free of symptoms or had symptomatic improvement 18 months after surgery however, at 40 months such improvement was maintained in only 83 8% of patients It was speculated that the failure to sustain clinical improvement was due to progression of atherosclerotic disease in the native coronary circulation or to late graft occlusion or both Others[15 1] have also observed late recurrence of symptoms after bypass surgery In the present study 98 patients had initially successful bypass surgery defined as angiographically demonstrated patency of all grafts just prior to hospital discharge During the early follow up period (< 3 months after surgery) all patients were reported free of angina pectoris Follow up *studies revealed that the most frequent factor* associated with recurrent angina pectoris was progressive coronary artery disease in the native circulation Such progressive disease as we have experienced may necessitate late reoperation[16 17] In 14 of the 38 patients with recurrent angina progressive coronary disease with the development of a complete new significant lesion was the only factor apparently responsible for recurrent symptoms In a study by Seides and co workers[15] 16 patients asymptomatic after bypass surgery were followed for five years In 11 late recurrent symptoms were observed In nine of these progressive disease of the *native coronary circulation* was found Seides and associates concluded that late symptomatic deterioration after bypass surgery is due for the most part to progressive disease in ungrafted vessels rather than to graft failure The present study in a larger group of patients confirms that conclusion

The frequency of progressive disease in ungrafted vessels was 24% *and the average* annual rate of progressive coronary disease was 10 7% of patients per year In other studies[5 21 2] the rate of progressive coronary artery disease has varied from 6% to 12% of patients per year Thus it might be anticipated that after five years half the patients undergoing bypass surgery will develop new significant lesions in ungrafted vessels However such speculation is unwarranted since the patients studied were a select group The majority (66%) demonstrating such progressive disease were evaluated for recurrent angina pectoris Thu the rate of progressive disease was 19 6% per year for patients with recurrent symptoms compared to only 6 7% asymptomatic patients per year

Our findings and other observations[1 2] indicate that coronary bypass grafts do not predispose to progressive occlusion of segments of the coronary arteries distal to the anastomoses Lawrie and associates[1] observed only a l[illegible] incidence of new distal lesions in grafted vessels five years after surgery McLaughlin and associates[2] have reported similar experience The uncommon occurrence of new significant lesions distal to graft sites and the more frequent occurrence of progressive disease in nongrafted vessels (3% vs 24%) can be best explained by the predilection of atherosclerotic disease to localize in certain sites in the coronary arterial tree[?] Thus aortocoronary bypass grafts are placed *distal to these most vulnerable sites* where significant lesions are already present In contrast ungrafted arteries are vulnerable at these proximal sites to atherosclerotic disease Progressive disease proximal to graft anastomoses is very common especially in the presence of high degree (> 90%) stenosis[16 ?] Such proximal disease appears to occur early after surgery with [illegible] subsequent progression after one year Thus five year follow up reveals little or no difference in the severity of the disease in proximal segments of grafted vessels compared with nongrafted arteries

Factors which may influence the frequency of progressive disease have been studied The frequency of progressive coronary artery disease was directly related to the time interval between the early and late study (Fig 1) indicating that such changes are time dependent This is consistent with observations reported by Bourassa and co workers[23] Thus at one year in nongrafted arteries *serial arteriographic* studies revealed a 7 3% frequency of progression compared to 41% at [illegible] years As in the present study hypertension diabetes mellitus cigarette smoking and family history was not observed[21 2 5] to influence the frequency of progressive coronary disease Some studies indicate that the progression of coronary disease may be influenced by serum lipid elevation[2 3] while others do not[21 22 2] In the study of Bemis and associates[2] plasma lipid elevation was significantly associated with both the frequency and severity of arteriographic progression compared to normolipemic individuals In a small series of patients reported by Ben Zvi and co

eagues[30] 44% of patients with progressive coronary disease had an elevated cholesterol compared to only 14% lacking arteriographic evidence of progression In the present study the mean serum cholesterol for the group with progressive disease was ($p < 0.05$) higher (Table II) In a pathological study by Lie and associates[31] hyperlipemia was associated with an increased frequency of atherosclerotic changes in the saphenous grafts Thus after one year 78 6% of grafts from hyperlipemic individuals revealed atherosclerotic changes compared to only 11 5% from normolipemic individuals

Incomplete surgical revascularization in most instances was the consequence of a completely blocked disease vessel without any evident run off Diffuse distal disease small vessel size or a distal vessel not identifiable at surgery were also common findings in patients with recurrent symptoms (Table I) It has been well documented[17 3] that symptomatic improvement accompanying bypass surgery is dependent upon the completeness of revascularization The initial improvement in our patients is not readily understood however only seven patients with recurrence of angina had incomplete revascularizaton as the only factor noted at late arteriographic study Finally the majority (61%) of instances of incomplete surgical revascularization were from our early surgical experience reflecting a more conservative initial approach

Several studies[33 37] indicate that most graft occlusions occur early whereas late graft occlusion is uncommon Late graft closure has been attributed in most instances to progression of the atherosclerotic process in the grafted artery[17] whereas early graft closure has been related to fibrous intimal hyperplasia [3] which does not appear to progress after the first year In our experience with 570 patients and 1 197 grafts early study (< 2 weeks postoperatively) revealed closure in 10 4% of grafts whereas in a follow up period ranging from five to 73 months (average 2 6 yrs) a further 7 7% of grafts closed In grafts found patent just prior to discharge from the hospital the average annual rate of subsequent closure (attrition rate) as reported by others has varied from 1 7% to 3 5% of grafts per year In the present study this average annual attrition rate was 3% per year with 5 6% annually in those presenting with recurrent angina compared to only 1 1% in those without recurrent pain In only four instances (10 5%) was late graft closure the only factor related to recurrence of angina In only one case was late graft stenosis found as an isolated finding In 5% of our cases (or 3% of grafts) late graft stenosis was observed comparable to the incidence reported by others[33 3] and probably related to surgical technique[3]

The present study indicates that progressive coronary artery disease is the major factor related to recurrent angina pectoris after coronary bypass surgery Late graft closure which is not common may also be associated with recurrent symptoms and may be related to progressive disease in distal recipient vessels Some evidence indicates that lipid abnormalities may favor the progression of the atherosclerotic process It is thus evident that risk factors especially lipid abnormalities warrant continued attention after successful surgical revascularization Incomplete surgical revascularization will always remain a factor favoring recurrent symptoms as a result of surgical limitations imposed by the vascular anatomy Early graft closure will continue to depend on such factors as size of vessels and run off variables which cannot be controlled However the major factor limiting sustained symptomatic relief after bypass surgery appears to be progression of the underlying atherosclerotic process

Summary

Arteriographic correlates of recurrent angina pectoris were obtained in 98 patients undergoing both early (< 2 weeks) and late (five to 70 months average 2 6 yrs) postoperative angiography after coronary bypass surgery All patients were discharged with arteriographic evidence of patency of all grafts (171 saphenous vein and six internal mammary artery) and all were asymptomatic during their early (< 3 month) postoperative follow up During late follow up recurrent angina occurred in 38 patients The group with recurrent angina had significantly higher frequencies of progressive coronary disease (47% vs 18%) incomplete surgical revascularization (35% vs 15%) and graft closure (21% vs 5%) compared to the asymptomatic group In the total study group 29 (30%) had progressive coronary disease with 16 (55%) having recurrent symptoms Progressive coronary disease was present in 24% of ungrafted vessels compared to only 3% in native coronary arteries distal to graft anastomoses The frequency of progressive coronary disease was

directly related ($p < 0.025$) to the time interval between early and late arteriographic studies The average annual rate of progressive disease was 10 7% of patients per year Patients with progressive coronary disease had a higher ($p < 0.05$) cholesterol (264 ± 57 vs 239 ± 37 mgm/dl) *Incomplete surgical revascularization* was more common (61%) in patients operated on during the early (< 1 5 yrs) experience with bypass surgery Late graft closure occurred in 7 6% of all grafts and in 11% of patients The average annual rate (attrition rate) of graft closure was 3% per year Late graft stenosis occurred in 5% of patients but was related to angina *pectoris in only one patient*

The present study indicates that late recurrent symptoms may be anticipated after bypass surgery since for the most part they are due to progressive atherosclerotic process in the native circulation Primary graft failure plays only a minor role in producing recurrent symptoms Thus continued control of risk factors especially *lipid abnormalities is warranted after bypass* surgery

The authors would like to acknowledge the kind assistance given by Brenda Hamby in preparing this manuscript

REFERENCES

1 Miller D C Cannom D S Fogarty T J Schroeder J S Daily P O and Harrison D C Saphenous vein coronary artery bypass in patients with Preinfarction Angina Circulation47 234 1973
2 Hamby R I Wisoff B G Kolker P and Hartstein M Intractable angina pectoris in the 65 to 79 year age group A surgical approach Chest 64 46 1973
3 Favaloro R G Effler D B Cheanvechai, C Quint R A and Sones, F M Jr Acute coronary insufficiency (impending myocardial infarction and myocardial infarction) Surgical treatment by the saphenous vein graft technique Am J Cardiol 28 598 1971
4 Mathur V S Guinn G A Anastassiodes L C Chahine R A Korompai F L Montero A C and Luchi R J Surgical treatment for stable angina pectoris. Prospective randomized study N Engl J Med 292 709 1975
5 Morris G C Reul G J Howell J F Crawford E S Chapman D W Beazley H L, Winters W L Peterson P K and Lewis, J M Follow up results of distal coronary artery bypass for ischemic heart disease Am J Cardiol 29 180 1972
6 Rees, G Bristow J D Kremkau F L Green C S Herr R H Griswald H F and Starr A Influence of aortocoronary bypass surgery on left ventricular performance N Engl J Med 284 1116 1971
7 Hamby R I, Tabrah F Aintablian A Hartstein M L, and Wisoff B G Left ventricular hemodynamics and contractile pattern after aortocoronary bypass surgery Factors affecting reversibility of abnormal left ventricular function Am Heart J 88 149 1974
8 Chatterjee K, Swan, H J C Parmley W W Sustaita H Marcus H and Matloff J Depression of left ventricular function due to acute myocardial ischemia and its reversal after aortocoronary saphenous-vein bypass, N Engl J Med 286 1117 1972
9 Saltiel J Lesperance J Bourassa M G Castonguay Y, Campeau L and Grondin P Reversibility of left ventricular dysfunction following aortocoronary bypass grafts Am J Roentgenol 110 739 1970
10 *Selden R Neill W A Ritzmann L W Okies J E* and Anderson R P Medical versus surgical therapy for acute coronary insufficiency N Engl J Med 293 1329 1975
11 Russell R O Moraski R E Kouchoukos N Karp R Mantle J A and Rackley C F Unstable angina pectoris national cooperative study group to compare medical and surgical therapy I Report of protocol and patient population Am J Cardiol 37 896 1976
12 Olinger G N Bonchkek L I Keelan M H Jr Tresch D D Siegel R Bamrah V and Tristani F *Unstable angina The case for operation Am J Cardiol* 42 634 1978
13 Schroeder J S Lamb I Hu M and Simson, E B Coronary bypass surgery for unstable angina pectoris Long term survival and function JAMA 237 2609 1977
14 Campeau L Corbara F Crochet D and Petitclerc R Left main coronary artery stenosis. The influence of aortocoronary bypass surgery on survival Circulation 57 1111 1978
15 Seides, S F Borer J S Kent K M Rosing D R McIntosh C L and Epstein S E Long term anatomic fate of coronary artery bypass grafts and functional status of patients five years after operation N Engl J Med 298 1213 1978
16 Lawrie G M Morris G C Jr Howell J F Ogura J W Spencer W H Cashion W R Winters W L Beazley H L Chapman D W Peterson P K and Lie J T Results of coronary bypass more than 5 years after operation in 434 patients Clinical treadmill exercise and angiographic correlations, Am J Cardiol 40 665 1977
17 Sheldon W C Rincon G Pichard A D Razavi M Cheanvechai C and Loop F D Surgical treatment of coronary artery disease pure graft operations, with a study of 741 patients followed 3 7 yr Progr Cardiovasc Dis 18 237 1975
18 Aintablian A Hamby R I Hoffman I Weisz D Voleti C and Wisoff B G Significance of new Q waves after bypass grafting Correlations between graft patency ventriculogram and surgical venting technique Am Heart J 95 429 1978
19 Hamby R I Angina pectoris A clinical-electrocardiographic angiographic correlative study in 510 patients in Rios J C editor Cardiovascular Clinics Clinical Electrocardiographic Correlation Philadelphia 1977 F A Davis Company pp 79 100
20 Goldstein J L Hazzard W R Schrott H G Bierman E L Motulsky A G Levinski M J and Campbell E D Hyperlipidemia in coronary heart disease I Lipid levels in 500 survivors of myocardial infarction J Clin Invest 52 1533 1973
21 Robert E W Guthaner D F Wexler L and Alderman E L Six year clinical and angiographic follow up of patients with previously documented complete revascularization Circulation 58(Suppl I) 194 1978
22 McLaughlin P R, Berman N D Morton, B C Schwartz L and Morch J F Longterm angiographic assessment of the influence of coronary risk factors on native coronary circulation and saphenous vein aortocoronary grafts Am Heart J 93 327 1977

23 Frick M H Valle M Harjola P T and Korhola O Changes in native coronary arteries after coronary bypass surgery Role of graft patency serum lipids and hypertension Am. J Cardiol 36 744 1975

24 Itscoitz, S Redwood D R., Stinson E B Reis, R. L., and Epstein S E Saphenous vein bypass grafts long term patency and affect on the native coronary circulation Am J Cardiol. 36 739 1975

25 Bourassa M G Lesperance J Corbara F., Saltiel, J and Campeau L. Progression of obstructive coronary artery disease 5 to 7 years after aortocoronary bypass surgery Circulation 58(Suppl 1) 100 1978

26 Rodriguez F L. Robbins, S L., and Bavasiewicz M Postmortem angiographic studies on the coronary arterial circulation Incidence and topography of occlusive coronary lesions relation to anatomic pattern of large coronary arteries, AM HEART J 68 490 1964

27 Berger R L., and Stary H C Anatomic assessment of operability by saphenous-vein bypass operation in coronary artery disease N Engl. J Med 285 248 1971

28 Kimbiris, D Lavine P., Van Den Broek H Najmi, M and Likoff W Devolutionary pattern of coronary atherosclerosis in patients with angina pectoris Coronary arteriographic studies, Am J Cardiol 33 7 1974

29 Bemis C E., Gorlin R Kemp H G., and Herman M V Progression of coronary artery disease A clinical arteriographic study Circulation 47 455 1973

30 Ben Zvi J., Hildner F J Javier R P., Fester A and Samet P Progression of coronary artery disease Cinearteriographic and clinical observations in medically and surgically treated patients Am J Cardiol. 34 295 1974

31 Lie J T., Lawrie G M and Morris, G C Aortocoronary bypass saphenous vein graft atherosclerosis. Anatomic study of 99 vein grafts from normal and hyperlipoproteinemic patients up to 75 months postoperatively Am J Cardiol 40 906 1977

32. Morris, G C., Jr., Reull, J F., Lowell, J F., Crawford E S Chapman, D W., Beazley H L., Winters W L., Peterson P K., and Lewis J M.. Follow up results of distal coronary bypass for ischemic heart disease Am. J Cardiol 29 180 1972.

33 Unicchio J F., and Bentivoglio L. G.. Patency of saphenous vein grafts five or more years after coronary bypass surgery Am. J Med 65 619 1978

34 Lesperance J Bourassa M G Saltiel, J., Campeau L., and Grondin C M. Angiographic changes in aortocoronary vein grafts Lack of progression beyond the first year Circulation 48 633 1973

35 Lawrie G M., Lie J T., Morris, G C., Jr., and Beazley H L. Vein graft patency and intimal proliferation after aortocoronary bypass early and long term angiopathologic correlations, Am J Cardiol 38 856 1976.

36 Campeau L., Lesperance J., Corbara F., Hermann, J., Grondin C M., and Bourassa, M G Aortocoronary saphenous vein bypass graft changes 5 to 7 years after surgery Circulation 58(Suppl. 1) 170 1978

37 Kouchoukos N T., Karp R B., Oberman A., Russell, R O., Jr., Alison H W., and Holt J H., Jr Long term patency of saphenous veins for coronary bypass grafting Circulation 58(Suppl. 1) 96 1978

38 Campeau L., Crochet D., Lesperance J., Bourassa, M G., and Grondin, C M Postoperative changes in aortocoronary saphenous vein grafts revisited Angiographic studies at two weeks and at one year in two series of consecutive patients, Circulation 52 369 1975

The effect of allopurinol on the degree of early myocardial ischemia

William L Arnold M S
Richard A DeWall M D, F A C C
Paul Kezdi M D, F A C C
Hans H J Zwart, M D
Dayton Ohio

The ultimate size of a myocardial infarction depends on the degree and duration of reduced blood flow to cells within the affected myocardium during an acute ischemic episode Following obstruction of blood flow in a major coronary artery the resulting hypoxic condition downstream from the obstruction rapidly leads in sequence to reversible myocardial injury irreversible injury and ultimate necrosis [1,2] The onset of irreversible myocardial damage probably occurs after 20 to 40 minutes of hypoxia and appears to proceed outward from the center of the involved area Recent interest in minimizing ultimate infarct size has centered around methods of salvaging the reversibly injured ischemic cells surrounding the central zone

Within the last decade several drug interventions such as glucose insulin potassium infusion corticosteroids nitroglycerin propranolol etc have been studied for their effectiveness in protecting the ischemic myocardium [3-6] Another drug that has been studied is the xanthine oxidase inhibitor allopurinol Because of its inhibitory effect on xanthine oxidase allopurinol effectively blocks the production of serum uric acid For this reason it has long been used for the treatmen gout From earlier experiments of Crowell associates [7] it was proposed that these enz inhibitory properties of allopurinol may pro cell viability during hypoxia and thus protect myocardium following coronary artery occlus We have reported evidence in animal experim for protection of the ischemic myocardium well as the ischemic kidney [9] by pretreatment allopurinol Treatment after occlusion was i fective as was also reported by others [10]

It was shown that early in the ischemic epis the reduced oxygen supply rapidly increases dephosphorylation of high energy phosph within the ischemic area [11] This process conti with the further breakdown of functional nuc tides terminating in the irreversible conversio xanthine to uric acid by xanthine oxidase [11] irreversible degeneration of adenine nucleot due to impaired oxidative phosphorylation oc only after 25 to 30 minutes of ischemia as shown by Vary and Schaffer [12]

Since all of the breakdown reactions of AT xanthine are initially reversible it was hypo sized that by blocking the conversion of xant to uric acid through xanthine oxidase inhib (with allopurinol) a mass action effect wo occur effectively retarding the further br down of functional nucleotides in the ische myocardium This would preserve the purine for subsequent rebuilding when the oxygen ply to the ischemic area was improved allopurinol also has vasodilatory effects felt that this property of the drug may a

From Wright State University School of Medicine Cox Heart Institute Dayton Ohio

Supported by National Institutes of Health, Department of Health, Education & Welfare Contract No N01 HV [illegible]

Received for publication April 9 1979

Accepted for publication July 20 1979

Reprint requests William L Arnold M S Wright State University School of Medicine Cox Heart Institute 3 [illegible] Southern Blvd Dayton Ohio 45429

restoring favorable oxygen conditions through enhancement of collateral blood flow to the ischemic area

The present study was undertaken to determine whether allopurinol will reduce the volume of ischemic myocardium in acute open chest experiments on dogs whose mid left anterior descending coronary artery (LAD) had been ligated.

Methods

Adult mongrel dogs of both sexes weighing 18 to 25 kilograms were used for these experiments The animals were anesthetized with sodium thiopental (12 mg/kg of body weight) They were intubated and respiration was maintained with a Harvard respirator After the chest was opened via a left lateral thoracotomy the pericardium was opened and the edges were sutured to the inner chest wall A Statham electromagnetic flow probe was placed around the ascending aorta to measure cardiac output Under fluoroscopic control catheters were placed in both the left and right femoral arteries and their tips were advanced into the left ventricle and central aorta respectively to monitor pressures from these sites Another catheter was advanced via the coronary sinus into the great cardiac vein for the withdrawal of blood samples A fourth catheter was placed in the femoral vein for withdrawal of peripheral blood samples Finally a No 2 0 silk suture was placed around the mid left anterior descending coronary artery below the septal and first diagonal branches for subsequent ligation

To observe the effect of allopurinol on the ischemic myocardium when the drug was administered either orally or intravenously both prior to and following ligation of the LAD the dogs were randomly divided into four groups

1 Control Group (13 dogs) No drug intervention either before or after ligation of the mid LAD

2 Post Ligation Allopurinol Treated Group (12 dogs) A continuous intravenous drip of sodium allopurinol was started approximately 20 seconds after ligating the mid LAD and administered at a rate of 16 mg/minute for the entire two hour post ligation period

3 Pre Ligation Allopurinol Orally Treated Group (six dogs) 400 mg Zyloprim (sodium allopurinol) was administered orally per day for five days prior to experiments In addition continuous intravenous drip of allopurinol was started in this group approximately 20 seconds after ligating the mid LAD and was continued through the two hour post ligation period at a rate of 16 mg/minute (as in Group 2)

4 Pre Ligation Allopurinol Intravenous Treated Group (six dogs) Continuous intravenous drip of allopurinol was started approximately 90 minutes prior to ligating the LAD and was continued through the two hour post ligation period at a rate of 10 mg/minute

With the exception of the three different drug intervention regimes the same protocol was used for all experiments and the following measurements were obtained

Hemodynamic Heart rate mean central aortic pressure left ventricular systolic pressure left ventricular end diastolic pressure left ventricular dP/dt (electronically derived) cardiac output and total peripheral resistance (mathematically derived)

Biochemical Electrolytes (Na K Cl, Ca Mg) total creatine phosphokinase free fatty acids glucose serum uric acid total inorganic phosphates lactate and pyruvates were obtained in arterial blood from the base of the aorta

Prior to ligation of the mid LAD baseline hemodynamic recordings were obtained and blood samples were drawn for biochemical measurements Following ligation the same hemodynamic and biochemical variables were recorded and samples at 30 seconds 5 minutes 30 minutes 1 hour and 2 hours post ligation After obtaining the two hour recordings and samples fluorescein dye was injected into the left ventricle via the LV catheter with the heart beating in situ This caused unaffected portions of the myocardium to be perfused with the dye and the nonperfused (ischemic) areas to remain free of dye The heart was then arrested with an injection of 20 mEq KCl into the left ventricle (approximately one minute after the fluorescein injection) The heart was immediately excised quick frozen in liquid freon (−40° C) freeze dried and cross sectioned from apex to base Subsequent viewing of the cross sections under ultraviolet light clearly defined the perfused (dye stained) areas as greenish gold in color The nonperfused areas of the myocardium appeared dark blue Planimetry was then used to measure the nonperfused areas seen

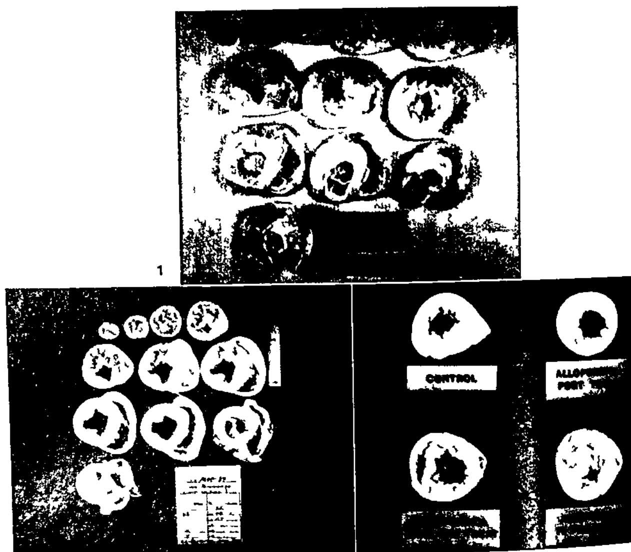


Fig 1 Control heart stained with fluorescein dye freeze dried and serially cross sectioned apex to base *Light green areas* (fluorescein stain) are normally perfused areas *Dark blue areas* are nonstained ischemic areas. Not large anterior and apical areas of nonperfusion Some perfusion of immediate subepicardial zone is present

Fig 2 Allopurinol intravenously pretreated heart prepared in same manner as control heart in *Fig 1* Note th smaller patchy diffuse areas of ischemia *(nonstained blue areas)*

Fig 3 Comparison of fluorescein dye staining of a single heart section from each of four groups studied. Eac section taken from approximately the same level of each heart (1 4 cm from apex)

on the surface of each section When this was combined with the thickness of the section the volume of the ischemic myocardium could be calculated

Statistical analysis

All hemodynamic biochemical and tissue data obtained during the study were analyzed for derivation of mean values standard deviations and standard errors Subsequently two tailed Student t test analysis was used to determine the significance of any within group and between group differences In addition the stain section measurement data of ischemic subjected to a one way analysis of varis multiple range test for significance of l group differences

Results

Thirty seven successful experiments w pleted in which meaningful data were c An experiment was considered successf the animal maintained a stable hemo and biochemical state during the surgica

able I Calculated ischemic volume below mid LAD ligation in terms of percentage of the total ardium

	Allopurinol IV pretreat (n = 6)	Allopurinol oral pretreat (n = 6)	Control (n = 6)	Allopurinol post treat (n = 6)
	12.28	14 19	19 47	21.56
deviation	2 0	5 5	4 1	8 1

y phase of the experiment and survived liga on of the LAD for a sufficient period of time (at least 30 minutes) to obtain sufficient data for analysis Those dogs which failed to remain ynamically stable during the preparatory phase of the experiment were randomly distrib uted throughout all four groups and hence were not a consequence of the treatment method

A total of 24 hearts (six from each group) were perfused with fluorescein dye and were prepared in the manner described above for measurement of ischemic size In all cases the LAD was ligated at its mid point and the areas of ischemic involvement were measured planimetrically from slides of the serially cross sectioned hearts Fig 1 is an example of a control heart stained with fluorescein dye sectioned apex to base and viewed under ultraviolet light Fig 2 displays an allopurinol intravenously pretreated heart pre pared in the same manner

Table I summarizes the ischemic size data in terms of mean percentage of total myocardium affected below the ligation The mean percentage of myocardium that was ischemic below the ligation as determined by the fluorescein dye technique ranged from 14 19% to 21.56% of the total myocardium below the LAD ligation in the allopurinol oral pretreated control and allopurinol post treated groups respectively The allopurinol intravenously pretreated group showed the smallest area of ischemic involvement of 12 28%

Table II summarizes the Student t test analysis of the data in Table I as to the significance of change in the three treated groups compared to the control group This analysis indicates that only the allopurinol intravenously pretreated group showed a significant decrease in the calculated ischemic volume The difference represents a 36 74% reduction in ischemic size from the control group ($p < 005$) The same data were subjected to a one way analysis of variance which yielded a significant F ratio (5 30 3 2156 $p < 05$) The subsequent multiple range test indicated

Table II Percent difference in ischemic volumes between control and treated groups

	Allopurinol IV pretreat	Allopurinol oral pretreat	Allopurinol post treat
% difference from control	−36 74	−26.91	+11 00
p value	< 005	NS	NS

that the allopurinol oral pretreated control and allopurinol post treated groups represent a homogeneous subset (not significantly different) By contrast the same range test indicated that the allopurinol intravenously pretreated group was significantly different (smaller ischemic area) from the other three groups ($p < 05$) A graphic presentation of this analysis is shown in Fig 4

In addition to having a smaller volume of ischemic tissue the allopurinol intravenously pretreated group exhibited a difference in the configuration of the border zones of the ischemic area Fig 3 displays a single section from a representative heart of each of the four groups studied This clearly shows that the control and allopurinol post treated hearts have large solid wedge shaped areas of transmural involvement Both the allopurinol intravenously pretreated and allopurinol orally pretreated hearts show smaller patchy diffuse areas of non transmural involvement with islands of perfused tissue within the involved area In addition there are numerous fingerlike projections of perfused tissue penetrating the involved area from the periphery

In a few of the hearts (two) from each group postmortem pressure controlled injections were made of the coronary arteries using a radiopaque barium sulfate mixture Filling of the coronary artery with this material permitted subsequent radiographic visualization of the coronary artery

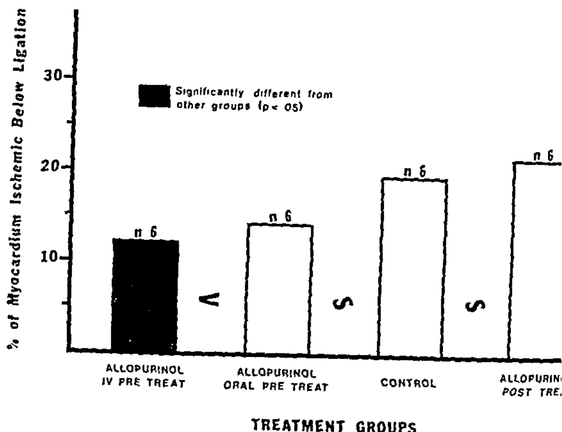


Fig 4 Comparison of mean percentage of ischemic injury of the myocardium below LAD ligation using ana of variance and Duncan s multiple range test

system and any collaterals when present Fig 5 shows a postmortem coronary angiogram in a control heart which was prepared in the manner described above (heart excised) While the figure presented here is two dimensional the original was a stereo radiograph In both the two and the three dimensional views there was no evidence of open collateral vessels to the distal LAD or its sub branches Fig 6 shows a similar postmortem coronary angiogram on a heart that was pre treated intravenously with allopurinol This radiograph shows *(arrows)* patent collaterals The obstructed LAD can be clearly seen as can the distal LAD filled retrogradely through collaterals from the distal branches of the circumflex coro nary artery

The hemodynamic measurements were done before and continued for two hours after LAD ligation when the dogs were sacrificed for fluores cein dye studies Heart rate was higher at baseline (before ligation) in the allopurinol intravenously pretreated dogs than in controls and remained above control values Early during post ligation there was a decrease in heart rate in all of the animals but it gradually returned t baseline However the difference be higher heart rate of allopurinol intr pretreated and controls persisted altho significant only at two hours post liga 7) The heart rate of the post ligation a animals did not differ from the control

Cardiac output was also higher befor in the allopurinol intravenously pretre than in controls while it was not differ the other groups (Fig 7) Cardiac decreased in all groups following liga remained suppressed except for the al intravenously pretreated dogs in whom i ly recovered toward baseline The dif however did not reach a level of sigr Mean arterial pressure showed a trend decrease from baseline to a lower level hours in both control and allopurinol nously pretreated dogs with no significar ence between them Calculated pe resistance was significantly lower before in the allopurinol intravenously pretreat while the other groups showed no differen

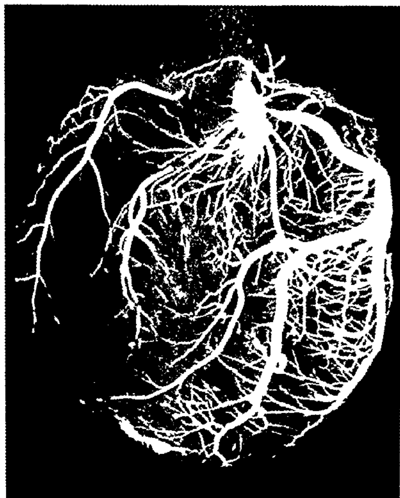


Fig 5 Postmortem radiographic visualization of the coronary artery system in a control experiment The arrow indicates the abrupt interruption of the filling of the LAD beyond the point of the ligature Note the lack of filling of the blood vessels beyond this point in the ischemic area

control (Fig 7) Following ligation there was a gradual increase of total peripheral resistance in all groups then a return toward baseline occurred In the allopurinol intravenously pretreated animals the resistance was again lower at two hours after ligation than with controls The left ventricular end diastolic pressure increased moderately in all groups following ligation and then returned toward baseline after two hours with no difference between the control and the treated groups

Of the 12 biochemical variables measured in arterial blood only three (uric acid total inorganic phosphates and calcium) showed significant differences between control and allopurinol intravenously pretreated animals over the two hour post ligation period (Table III) As can be seen in Table III the baseline values for these variables were also different and remained so for the entire two hour post ligation period This would indicate that the differences between groups were due to the drug s effect (allopurinol) and ischemia affected the biochemical variables in the same direction but not to a significantly different degree The other treated groups showed no significant differences in these measurements at baseline and two hours post LAD ligation Creatinine phosphokinase levels increased but because of prior thoracotomy this cannot be attributed to the ischemic injury alone

Discussion

The present findings indicate that allopurinol when given intravenously prior to ligation of the anterior descending coronary artery will decrease early ischemic injury (two hours after ligation) by



Fig 6 Postmortem radiographic visualization of the coronary artery system in an allopurinol pretreated dog *Arrow 1* indicates LAD filling at the point of ligation *Arrow 2* indicates retrograde filling of the LAD stump through collaterals from the circumflex artery *Arrow 3* indicates posterior descending branch of the circumflex coronary artery Note numerous small collaterals in the ischemic area (originally much more numerous when observed under direct vision but partially extracted by freeze drying to obtain the photograph)

36% when compared to control experiments This difference was significant to the p < 005 level The fluorescein injection technique appeared to be a reliable indicator of nonperfused ischemic areas of the myocardium As seen in Fig 3 the control animals (and allopurinol post ligation treated animals) showed solid wedge shaped areas of transmural absence of flow while in the allopurinol pretreated hearts there were only small patchy nontransmural areas of no flow with numerous fingerlike projections of perfused tissue penetrating into the nonperfused areas This suggests partial perfusion in the pretreated hearts from the peripheral border zones The islands of perfused areas appear to be projections of perfused areas from the epicardial zones viewed when they are turned perpendicular to the cross section of the viewed area

This difference between control and allopurinol pretreated hearts indicates that blood flow is partially maintained in the ischemic area in allopurinol pretreated animals This is probably due to a vasodilatory action of allopurinol opening up collateral blood vessels Such coronary (and general) vasodilatory effects have previously been demonstrated [13] Since allopurinol post treated hearts did not show this partially maintained circulation it must be inferred that the drug must be present in the coronary vasculature prior to onset of ischemia in order to be effective

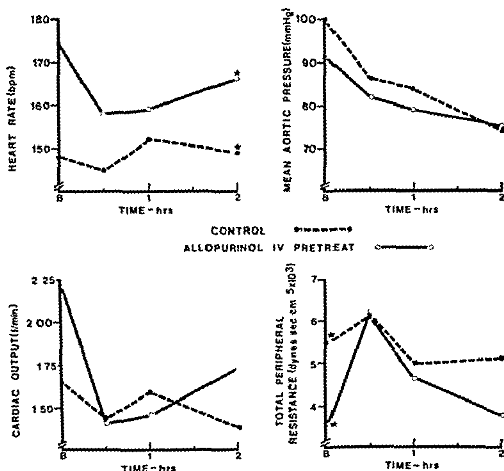


Fig 7 Changes in heart rate mean blood pressure cardiac output and calculated peripheral resistance from baseline values to two hours post LAD ligation *Asterisks* indicate significant differences with p values <0 05

Table III Biochemical changes in arterial blood before and after ligation of LAD

	Baseline	*30 minutes*	*1 hour*	*2 hours*
Uric acid				
Control	0 93 ± 0 46	1 13 ± 0.56	1 09 ± 0.55	1 19 ± 0 73
Allopurinol	0 33 ± 0 13	0 45 ± 0 13	0.50 ± 0 05	0 46 ± 0 10
Total inorganic phosphates				
Control	4.38 ± 1 20	4 30 ± 1 20	4 62 ± 1.20	4 88 ± 1.30
Allopurinol	2 32 ± 0.86	2 37 ± 0 83	2 44 ± 0 71	3 04 ± 0.82
Total CPK				
Control	76.9 ± 29 6	86 0 ± 30 8	90 17 ± 30 4	106.2 ± 29 7
Allopurinol	81 5 ± 49.9	91.2 ± 50 8	95.8 ± 53.9	110 8 ± 51 7
Serum calcium				
Control	10.39 ± 2 33	10.25 ± 2 59	9.37 ± 1 71	9.38 ± 1.51
Allopurinol	8 48 ± 0 65	8 10 ± 1 07	7 98 ± 0.8?	8.18 ± 0 76

$p < 0\ 05$

Evidence for functionally patent collateral blood vessels in the allopurinol pretreated hearts during the LAD ligation was also obtained by the postmortem pressure control injection of the coronary vasculature with a radiopaque BaSO mixture These injections were obtained by cannulating both the left and right main coronary arteries immediately after sacrificing the animal and excising the heart Since the injection pressure was monitored and kept at the diastolic pressure the animal had prior to sacrificing we believe this visualization of collaterals is not an artifact caused by an excessively high injection pressure The difference between the lack of collaterals in the control hearts and the effective collateralization in the allopurinol intravenously pretreated hearts was very impressive (Figs 5 and 6) Other investigators have shown that significant collateral blood flow cannot be demonstrated in the untreated ischemic myocardium of the dog for at least 18 hours after coronary artery occlusion [1] Also the demarcation of necrotic myocardium from normal is generally extremely sharp and the interdigitation of normal and necrotic tissue is presently only in the borderzone as previously described by Factor and co workers [5]

Hemodynamic changes following ligation of the LAD followed the usual pattern of depressed left ventricular function This consisted of an initial decrease of the heart rate mean arterial pressure and cardiac output and an increase of the peripheral resistance After two hours the changes tended to return toward baseline However in the allopurinol intravenously pretreated animals there was initially higher heart rate cardiac output and lower peripheral resistance indicating general vasodilation and compensatory increase of cardiac output The response to LAD ligation was similar to control namely initial decrease of heart rate blood pressure and cardiac output There was an eventual return toward the high baseline heart rate and cardiac output and low peripheral resistance in the allopurinol intravenously pretreated dogs The difference between control and pretreated animals was however statistically significant only for heart rate and peripheral resistance

The hemodynamic trend indicates that initially there is a depressed left ventricular function following LAD ligation which eventually subsides or is compensated for It is probable th initial depressed function is due to a combi of a mechanical element caused by the n tracting ischemic area and to reflex suppres cardiac function initiated by receptors i ischemic area itself [16] It has been shown tha reflexes may overcome attempts by sy baroreceptors to compensate for the dep hemodynamic factors due to the noncontr ischemic muscle [17] Apparently however reflex effects are soon compensated for a hemodynamic changes are returning toward trol after two hours Since the animals sacrificed at two hours secondary deteriorati the hemodynamics as often seen in an followed for longer periods following LAD tion was not observed

The changes in the control group durin time period of two hours were only trends were not statistically significant However changes in the allopurinol pretreated ani between baseline and 30 minutes as wel between 30 minutes and 2 hours were signifi and the differences at baseline and 2 h between control and allopurinol pretreated a mals were also significant This indicates that reflex suppression probably was very effectiv allopurinol intravenously pretreated animals 30 minutes That the hemodynamic suppress was reflex in origin is indicated by the ra return (after 2 hours) to the high levels of he rate cardiac output and low levels of periphe resistance in the allopurinol intravenously p treated animals This baseline and two-hour po LAD ligation difference seems to be the o significant difference in hemodynamics betwe the control and the pretreated animals Wh these changes are related to the fluorescein a radiographic perfusion studies they confirm th a pre-existing systemic (and coronary) vasodil tion must be present in the allopurinol intrave nously pretreated animals This is consistent wi the finding of partially perfused ischemic areas i the fluorescein studies and the open collaterals i the radiopaque mixture perfusion studies

The measured biochemical changes obtained i the arterial blood do not contribute significantl to the results The blood withdrawn was a mi ture of blood from the heart and the systemic circulation The results are therefore nonspecific regarding changes in the ischemic area Since no

CPK isoenzymes were obtained the CPK levels in open chest animals cannot be evaluated There was a difference in the uric acid levels at baseline and two hours in the control and allopurinol pretreated animals with the pretreated animals being much lower at both times This is expected since allopurinol lowers uric acid in the systemic circulation It is not possible to relate the minimal increases following LAD ligation to any local ischemic metabolic event in the heart muscle Any protective effect of allopurinol on myocardial nucleotides and purine bases through inhibition of degradation would have to be studied by direct analysis of adenine nucleotides in the ischemic myocardium itself

It is interesting to speculate on the mechanism of protection of the ischemic myocardium by allopurinol Allopurinol has been shown to have vasodilatory properties and could have a direct action on the coronary collaterals by keeping them at least in part open when blood flow through the normal channels to a segment of the myocardium is suddenly interrupted However it is also possible that allopurinol exerts its effect through prevention of irreversible loss of adenine nucleotides from the mitochondria Adenosine itself would act locally as a coronary vasodilator Further investigations are needed to determine the effect of ischemia on mitochondrial nucleotides in the myocardium and also how allopurinol modifies anerobic metabolism

Summary

The effect of allopurinol on the size of ischemic injury was evaluated following ligation of the left anterior descending coronary artery (LAD) in 37 open chest dogs Heart rate aortic blood pressure left ventricular pressure cardiac ouptut and total peripheral resistance were continuously monitored Arterial blood was obtained and analyzed for electrolytes enzymes uric acid total inorganic phosphates lactate and pyruvate before and after two hours of LAD ligation At two hours the hearts were perfused with fluorescein dye to delineate the flow/no flow areas of the excised cross section myocardium Planimetry and section thickness were used to calculate the volume of ischemic myocardium

Heart rate and cardiac output were higher and peripheral resistance was lower at baseline and two hours after ligation in the allopurinol intravenously pretreated dogs than in controls Uric acid was significantly lower at baseline and two hours after LAD ligation and lower levels of total inorganic phosphate calcium and magnesium were present at two hours after ligation The stained cross sectioned hearts showed that the control and postligation allopurinol treated animals had respective ischemic areas of 19 42% and 21 56% of the total myocardium below the section of the LAD ligation obtained perpendicular to the long axis of the heart In contrast animals pretreated with allopurinol whether orally or intravenously showed 14 19% and 12 28% ischemic areas respectively The latter represented 36 74% less ($p < 005$) than in the control group Postmortem angiographic studies performed on hearts from each group demonstrated collateral connections to the distal LAD in the allopurinol intravenously pretreated group and an absence of open collaterals in the control group

The study suggests that allopurinol pretreatment has a protective effect on the ischemic myocardium This is probably due to opening of coronary collaterals either by direct vasodilatory action or by maintaining locally high levels of adenosine by enzyme inhibition which in turn acts as a vasodilator

REFERENCES

1 Braunwald E and Maroko P Protection of the ischemic myocardium Hosp Pract **8** 61 1973
2 Cox J L., McLaughlin, V W., Flowers, N C., and Horan L. G The ischemic zone surrounding acute myocardial infarction Its morphology as detected by dehydrogenase staining AM HEART J **76** 650 1968
3 Brachfeld N Ischemic myocardial metabolism and cell necrosis Bull N Y Acad Med. **50** 261 1974
4 Maroko P R Libby P Sobel B E Bloor C M Sybers, H D Shell W E., Covell J W and Braunwald E Effect of glucose-insulin potassium infusion on myocardial infarction following experimental coronary artery occlusion Circulation **45** 1160 1973
5 Libby P Maroko P R Bloor C M Sobel B E and Braunwald E Reduction of experimental myocardial infarct size by corticosteroid administration J Clin Invest **52** 599 1973
6 Reimer K. A Rasmussen M M and Jennings, R B On the nature of protection by propranolol against myocardial necrosis after temporary coronary occlusion in dogs, Am J Cardiol **37** 520 1976
7 Crowell J W Jones, C E., and Smith E Effect of allopurinol on hemorrhagic shock Am J Physiol. **216** 744 1969
8 DeWall R A Vasko K A Stanely E L and Kezdi P Responses of the ischemic myocardium to allopurinol AM HEART J **82** 362 1971
9 Vasko K A DeWall R A., and Riley A M Effect of allopurinol in renal ischemia Surgery **71** 787 1972

10 Shatney C H Maccarter D J and Lillehei R C Effects of allopurinol propranolol and methylprednisolone on infarct size in experimental myocardial infarction Am J Cardiol 37 512 1976
11 Hitchings G H Effects of allopurinol in relation to purine biosynthesis Ann Rheum Dis 25 601 1966
12 Vary T and Schaffer S W Role of adenine nucleotides in ischemic injury Fed Proc 37 230 1978
13 Ellis C H Touw K B and Dickerson S W Some acute hemodynamic effects of large doses of sodium allopurinol in open chested dogs Arch Int Pharmacodyn Ther 205 355 1963
14 Cox J L Pass H I Wechsler A S Oldham H N and Sabiston D C Coronary collateral blood flow in acute myocardial infarction J Thorac Cardiovasc S 69 117 1975
15 Factor S M Sonnenblick E H and Kirk, E Histological borderzone of acute myocardial infarcti Islands or peninsulas? Am J Pathol 92 111 1978
16 Wyatt H L Forrester J S daLuz P L Diamond, A Chagrasulis R and Swan H J S Functi abnormalities in nonoccluded regions of myocardi after experimental coronary occlusion Am J Card 37 366 1976
17 Misra S N and Kezdi P Hemodynamic effects adrenergic stimulating and blocking agents in cardiog ic shock and low output state after myocardial inf tion Am J Cardiol 31 724 1973

ase reports

ıdden death ın cardıomyopathy Role of adycardıa dependent repolarızatıon changes

: K Bıssett M D
hn W Watson M D
mes A Scovıl M D
ıl De Soyza M D
ıvıd W Ohrt M D
tle Rock Ark

ıe ıncreased use of portable ECG recorders has rmıtted observatıons on the mechanısm of ıdden death ın coronary artery dısease Recent ɔorts have demonstrated ventrıcular fıbrılla ın [1 2] as well as sınus arrest precedıng death [3] ıe present report documents changes ın cycle ıgth and ectopıc actıvıty for 16 hours prıor to ntrıcular fıbrıllatıon ın a 20 year old patıent th cardıomyopathy Analysıs of the relatıon ıp of sınus rate couplıng ınterval and corrected Γ ınterval suggests that a unıque set of cırcum ances present for only a brıef perıod may have sulted ın ventrıcular fıbrıllatıon (VF)

The results demonstrate the ımportance of 'adycardıa-dependent changes ın repolarızatıon ıd ıllustrate the sıgnıfıcance of a post extrasys ılıc reductıon ın the prematurıty ındex

ase report

A 20-year-old black male was admitted to Unıversıty Hospı l because of crampıng abdomınal paın of 3 to 4 weeks ıratıon The patıent was allegedly ın good health untıl 1 onth prıor to admıssıon when he developed weakness and ortness of breath whıle employed as a constructıon worker he dyspnea was accompanıed by complaınts of nausea ɔmıtıng and abdomınal paın whıch dımınıshed wıth meals wo weeks prıor to admıssıon an upper gastroıntestınal serıes as saıd to be normal One week before admıssıon a chest fılm as performed by another physıcıan the patıent was advısed ıat hıs heart was enlarged The patıent contınued to ɔmplaın of epıgastrıc paın and vomıtıng accompanıed by the development of paroxysmal nocturnal dyspnea and was admıtted to the hospıtal. There was no past hıstory of gastroıntestınal or cardıac dısease The patıent admıtted to the consumptıon of 6 to 12 cans of beer a day There was no famıly hıstory of cardıac dısease four sıblıngs were saıd to be ın good health.

Physıcal examınatıon revealed a well-developed male ın no acute dıstress wıth a temperature of 99 4 F blood pressure of 120/90 and a pulse of 96 beats/mınute The optıc fundı were normal and the thyroıd was not enlarged. Examınatıon of the heart demonstrated a regular rhythm. The poınt of maxımum ımpulse was ın the anterıor axıllary lıne An S gallop was present and an S was descrıbed by a cardıac consultant. A grade 3/6 systolıc murmur along the left sternal border and at the apex was noted The lıver and spleen were not palpable and there was no pretıbıal edema

Admıssıon laboratory data ıncluded hemoglobın of 15 1 gm % hematocrıt of 45% and whıte count of 6 900 The BUN was 15 mg % sodıum 138 mEq /L., potassıum 4 5 mEq /L total proteın 5 3 gm % albumın 3 1 gm.% bılırubın 1 6 mg % amylase 95 nephelos/dl (normal 70 to 140) and normal urınalysıs A T was 7 6 µgs% ANA negatıve VDRL nonreac tıve dırect Coombs test negatıve and serum complement (C) 11 mg %

An electrocardıogram showed normal sınus rhythm wıth a rate of 81 beats/mınute wıth frequent premature ventrıcular contractıons (PVC s) voltage crıterıa for left ventrıcular hypertrophy and T ınversıon ın Leads I II aV$_L$ and V through V The QT ınterval was 380 msec. and QTc 0 44 second. A PA and lateral chest fılm showed marked cardıomegaly An echocardıogram showed a markedly dılated left ventrıcle (dıastolıc dımensıon 9 4 cm) wıth a calculated ejectıon fractıon of 21% The mıtral valve and aortıc valve appeared to be normal. Followıng admıssıon the patıent s rhythm was monıtored by telemetry Maalox was prescrıbed for abdomınal paın A gastroıntestınal work up ıncludıng a cıne esophagram and upper gastroıntestınal serıes wıth small bowel follow through was normal

A cardıology consultant made a dıagnosıs of cardıomyopa thy of unknown cause On the twelfth hospıtal day frequent multıfocal PVC s were noted A serum dıgoxın level was 0 95 ng /ml. The patıent was moved to the ıntensıve care unıt and gıven ıntravenous lıdocaıne wıth ımprovement ın hıs ventrıc ular arrhythmıa Oral quınıdıne 200 mg every 6 hours, was

'rom the Dep rtment of C rdıology Unıversıty of Arkansas for Medıcal Scıences

Received for publıc tıon Dec 19 19 8
Accepted fo publıcatıon Feb 16 1979

Reprınt requests Joe K. Bıssett, M D D partment of Cardıology Unıversıty of Arkansas f Medıcal Scıences, 4301 West Markham Lıttle Rock, Ark. 72201

)00?-8 03/80/050625 + 05$00 50/0 © 1980 The C V Mosby Co

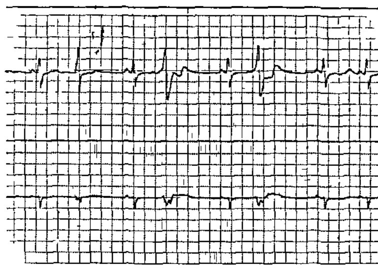


Fig 1 Sequence of PVC s at 2 15 A M The initial coupling interval was 720 msec Following the post-extrasystolic pause the coupling interval was reduced to 520 msec for the two following extrasystoles The cycle length was 840 msec QT 440 msec QTc 480 msec

Table I Tabulation of data from Holter monitoring (10 15 A M to 2 00 A M)

	No of PVC s /hr	*Heart rate (beats/ min)*	*RR interval (msec)*	*QTc (seconds)*	*Coupling interval (msec)*	*No of PVC s analyzed*	*Prematurity index*	*Coup[illegible] int[illegible] for p[illegible] PV[illegible] epis[illegible]*
10 A M to 11 A M	75	90 4 ± 3 8	660 ± 39	0 43 ± 0 02	443 ± 25	8	1 28 ± 0 05	48[illegible]
11 A M to 12 P M	149	90 ± 6 1	655 ± 47	0 44 ± 0 02	460 ± 63	24	1 25 ± 0 21	44[illegible]
12 P M to 1 P M	174	92 3 ± 8 1	635 ± 56	0 44 ± 0 01	430 ± 40	22	1.27 ± 0 13	44[illegible]
1 P M to 2 P M	326	89 4 ± 6 1	804 ± 46	0 45 ± 0 03	524 ± 89	35	1 25 ± 0 15	505 ± [illegible]
2 P M to 3 P M	243	93 2 ± 5 8	610 ± 20	0 43 ± 0 02	444 ± 47	28	1 30 ± 0 16	410 ± [illegible]
3 P M to 4 P M	73	81 7 ± 6 6	705 ± 40	0 44 ± 0 01	430 ± 38	16	1 18 ± 0 10	443 ± [illegible]
4 P M to 5 P M	57	90 ± 8 1	649 ± 50	0 44 ± 0 02	441 ± 20	20	1 30 ± 0 11	[illegible]
5 P M to 6 P M	113	89 ± 7 3	640 ± 60	0 46 ± 0 01	461 ± 80	15	1 25 ± 0 10	[illegible]
6 P M to 7 P M	164	89 1 ± 9	663 ± 60	0 44 ± 0 01	427 ± 30	35	1 27 ± 0 12	4[illegible]7 ± [illegible]
7 P M to 8 P M	771	92.4 ± 4 2	629 ± 30	0 43 ± 0 01	431 ± 20	65	1 25 ± 0 08	431 ± [illegible]
8 P M to 9 P M	332	93 4 ± 6 5	634 ± 45	0 44 ± 0 02	439 ± 50	47	1 29 ± 0 14	4[illegible]1 ± [illegible]
10 P M to 11 P M	234	78 ± 8 5	768 ± 30	0 48 ± 0 03	581 ± 50	35	1 36 ± 0 11	600[illegible]
11 P M to 12 P M	29	70 1 ± 3 4	818 ± 30	0 47 ± 0 03	538 ± 0 16	8	1 25 ± 0 29	5[illegible]0 ± [illegible]
12 P M to 1 A M	42	72 ± 4 4	791 ± 80	0 43 ± 0 01	522 ± 0 09	20	1 39 ± 0 25	460 ± [illegible]
1 A M to 2 A M	159	68 2 ± 4 9	804 ± 50	0 45 ± 0 03	524 ± 89	35	1 30 ± 0 25	505 ± [illegible]

initiated on the sixteenth hospital day and given at 9 A M 3 P M 9 P M and 3 A M The final quinidine dose was 5 to 6 hours before death Digoxin 0 25 mg /day was given from the fifth through the twelfth hospital day Digoxin was then discontinued on the thirteenth day No digitalis was given until the seventeenth day when the patient received 0 25 mg orally On the eighteenth hospital day 0 25 mg digoxin was given orally at 9 A M and 9 P M The final digoxin dose was given 5 to 6 hours before death.

On the eighteenth hospital day a Holter monitoring was applied at approximately 10 15 A.M to follow the progress of his ventricular arrhythmia Serum electrolytes on the eighteenth hospital day included a serum sodium of 140 mEq /L potassium 3 9 mEq /L, chloride 97 mEq L and CO 37 mEq /L. At 2 25 A M on the nineteenth day vent[illegible] fibrillation was noted by telemetry Cardiopulmonary [illegible] tation was initiated but was unsuccessful and the pati[illegible] pronounced dead at approximately 4 00 A.M

At autopsy the heart weighed 610 grams The left ve[illegible] appeared to be dilated left ventricular thickness was [illegible] There was no evidence of coronary atherosclerosis o[illegible] matic valvular disease The circumference of the aorta [illegible] level of the arch was 4 5 to 5 cm Microscopic examina[illegible] the myocardium revealed no specific etiology for the p[illegible] cardiomegaly No inflammatory infiltrate or significant [illegible] of fibrosis were seen The remainder of the autopsy da[illegible] noncontributory no explanation for the patient s gastr[illegible] tinal symptoms was found

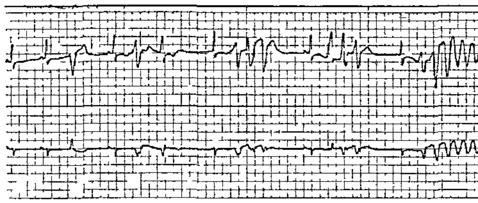


Fig 2 Terminal event at 2 19 A M A PVC with a coupling interval of 600 msec is followed by a sinus beat and a PVC at an interval of 460 msec Paired PVC s result followed by two three beat episodes of ventricular tachycardia The final extrasystole has a coupling interval of 440 msec and precipitates ventricular fibrillation Note that there is a tendency for the prematurity index to shorten following the post-extrasystolic pause The prematurity index for the final seven ectopic beats (first PVC of each sequence) was 1.52, 1 38 1 36 1 07 0 98 and 0 98 respectively The last ectopic beat with an index of 0 98 initiates ventricular fibrillation This PVC had the shortest prematurity index observed during the 16-hour period and coincided with a QTc equal to the longest value measured.

Table II Tabulation of data from Holter monitoring (2 15 A M to 2 19 A.M)

	No of PVC s/ min	RR interval (msec)	QTc (sec)	Coupling interval (msec)	No of PVC s analy ed	Prematurity index	Coupling index for paired PVC s/episodes
? 15 A.M	3	880 ± 40	0 47 ± 0 01	587 ± 115	3	1.33 ± 0 27	0
2 16 A.M	1	936 ± 38	0 46 ± 0 01	460	1	1 70	0
2 17 A M	4	884 ± 41	0 47 ± 0 01	740 ± 167	4	1 64 ± 0 37	0
2 18 A M	1	852 ± 18	0 47 ± 0 0?	660	1	1.50	0
2 19 A.M	7	888 ± 44	0 48 ± 0 02	531 ± 99	7	1 19 ± 0 22	460/1

*The final sinus beat oc rred at approxim t ly 19 minutes and 57 seconds.

Analysis of Holter recording

Heart rate was measured at 1 minute intervals from a histogram beginning at approximately 10 15 A M and extending to the onset of ventricu lar fibrillation at approximately 2 20 A M The number of premature ventricular beats per hour was detected by an automated recording system * At 10 minute intervals for the 16 hour period ECG strips of approximately 1 minute duration were obtained The cycle length and QT interval were obtained from five beats in each sample and the corrected QT intervals (QTc) calculated as the QT interval in seconds divided by the square root of the cycle length in seconds The coupling interval of all premature ventricular beats was measured in milliseconds as well as the coupling interval of paired ventricular beats and R R intervals during three consecutive ventricular ectopics The prematurity index was measured as the coupling interval divided by the QT interval of the preceding sinus beat All data for the first 16 hours were tabulated at hourly intervals (Table I) During the final hour a continuous recording of the 5 minutes preceding the terminal episode was made For purposes of this study only the first of a two or three beat sequence was counted in the sample group as a PVC The coupling intervals of the initial beats are shown in Table I The automated recording however in cluded all ventricular extrasystoles

The results are shown in Tables I and II The total number of ventricular ectopic beats tabu lated by the automated recorder was 3 368 from hours 10 00 A M until 2 00 A M During this period a total of 411 PVC s (13%) were analyzed from sample rhythm strips

*Del Mar Avi nics, Irvine Calif

The corrected QT interval did not remain constant over the range of R R intervals shown There was a significant increase in the QTc at increasing cycle lengths During the 9 hours with mean sample cycle lengths of less than 680 msec the mean QTc interval exceeded 0 44 second in only one instance (5 to 6 P M) The mean QTc interval was greater than 0 44 second in 6 of 8 hours with a cycle length greater than 680 msec ($p < 0\ 05$ by Fisher s test) During the 5 minutes immediately preceding death cycle length ranged from 852 to 936 msec and the QT interval varied from 0 46 to 0 48 second during the minute in which the terminal event occurred The QTc interval during the final minute was equal to the longest QTc recorded (0 48 second from 10 to 11 P M)

Table I demonstrates that ectopic coupling intervals tended to increase at longer cycle lengths so that the prematurity index tended to remain relatively constant from 10 00 to 2 00 A M with the exception of 3 00 to 4 00 P M when the prematurity index was 1 18 ± 0 10 During the final minute however there was a decrease in the prematurity index to 1 19 ± 0 22 msec for the seven PVC s Reference to Fig 2 shows that the prematurity index of the final seven ectopic beats was 1 52 1 38 1 36 1 03 1 07 0 98 and 0 98 respectively The last PVC with an index of 0 98 initiates VF The final PVC had both the shortest prematurity index measured during the 16 hours and occurred when the QT interval was equal to the longest value obtained A reduction in the coupling interval following a post extrasystolic pause is shown in Figs 1 and 2

The coupling intervals associated with paired PVC s are shown in the last column of Tables I and II Not shown are the initial coupling intervals (424 ± 46 msec) for five episodes of three consecutive ventricular ectopic beats which occurred between 10 00 and 2 00 A M (two episodes during hour 7 to 8 and one each during hours 8 to 9 11 to 12 and 12 to 1)

Discussion

The occurrence of ventricular fibrillation during the early morning hours of the nineteenth hospital day was unexpected There was no obvious clinical event which produced the terminal arrhythmia Ventricular fibrillation developed during a period of limited activity and increased cycle length and was preceded by 4 minutes during which the number of ectopic beats per minute was less than five

Analysis of cycle length corrected QT interval and prematurity index suggests several factors which may have led to ventricular fibrillation First the QTc was prolonged (0 48) during the final minute and was equal to the longest QTc interval observed during the previous 16 hours The association of a prolonged QT interval and increased tendency to ventricular arrhythmias in a congenital[4, 5] or acquired abnormality[6] is well known, and a recent report has emphasized the value of QTc prolongation as a predictor of sudden death following myocardial infarction. An increased incidence of QTc abnormalities in survivors of out of hospital fibrillation has also been described[8] The explanation for increased repolarization abnormalities in this patient during longer cycle lengths is unknown a similar analysis of changes in QTc with cycle lengths in patients with ventricular arrhythmias could not be found

The prematurity index of the PVC initiating ventricular fibrillation and preceding PVC was less than the index of any PVC observed during the 16-hour period Although the mean prematurity index from the sample group between 3 and 4 P M was 1 18 ± 0 10 msec the mean QTc interval at that time was considerably less 0 44 second The combination of a QT interval of 0 48 second and a prematurity index of less than 1 occurred only during the final minute This unique set of circumstances probably precipitated ventricular fibrillation

Progressive shortening of the coupling interval following a post extrasystolic pause was observed during the final minute as well as one preceding sequence (Fig 1) The significance of this phenomenon in human ventricular arrhythmias is unknown but a reduction in coupling interval may represent a rate related decrease in the conduction time of a reentrant pathway There was no additional evidence to suggest the presence of parasystolic focus

The importance of coupling intervals or the R on T phenomenon has been challenged by reports from several investigators[9-11] These studies have shown that ventricular tachycardia may be initiated from relatively long as well as short coupling intervals Information obtained by the use of the extrastimulus technique[12] however has shown that a critical range of coupling intervals, whether long or short is frequently required for the production of ventricular tachycardia There is insufficient evidence to extend these observa

tions to the production of ventricular fibrillation it appears reasonable that both a decrease in the fibrillation threshold perhaps produced by repolarization abnormalities[1] and a critical coupling interval may be required

During the final 2 days of the patient s hospitalization both digoxin and quinidine were administered Recent studies have shown that serum digoxin levels may be increased in patients given quinidine[15] accompanied by clinical manifestations of digitalis intoxication Although the mechanism has not been established alterations in digoxin binding have been suggested[15] The effects of digoxin quinidine interaction in this patient are unknown Although serum digoxin levels were not measured during the final 6 days the patient received only three doses of digoxin during this time

The presence of quinidine intoxication cannot be excluded Prolongation of the QT interval by quinidine is well known[16] and recent reports emphasize the continuing problem of arrhythmias in patients with quinidine excess[17, 18] It should be noted that quinidine intoxication might not have been required to produce harmful effects since the QT interval was already prolonged Additional repolarization changes may have facilitated the occurrence of ventricular arrhythmias

The patient described in this report was a young man with a history of heavy ethanol intake who presented with abdominal pain and frequent PVC s In spite of multiple sinus rates and coupling intervals the combination of excessive QT prolongation and prematurity index of less than 1 was found only during 1 minute and was associated with ventricular fibrillation Analysis of the Holter recording suggests that measurement of QT interval and prematurity index at multiple rates may be required to assess the risk of ventricular arrhythmias in similar instances

Summary

A 20 year old man presented with cardiomegaly frequent PVC s and abdominal pain On the nineteenth hospital day the patient developed ventricular fibrillation and died Analysis of a Holter recording initiated 16 hours previously demonstrated an increase in the corrected QT interval (QTc) to 0 48 second and a prematurity index less than 1 0 only during the minute terminated by ventricular fibrillation

This report documents changes in sinus rate coupling interval QTc and prematurity index for 16 hours preceding ventricular fibrillation in a patient with cardiomyopathy The timing of the terminal arrhythmia coincided with significant changes in the QTc and prematurity index characterized by bradycardia dependent QTc prolongation and a post extrasystolic reduction in prematurity index

REFERENCES

1 Gradman A H., Bell P A and DeBusk R F Sudden death during ambulatory monitoring clinical and electrocardiographic correlations Circulation **55** 210 1977
2. Pool J Kunst K and Van Wemeskeren J L Two monitored cases of sudden death outside hospital, Br Heart J **40** 627 1978
3. Bleifer S B., Bleifer D J., Hansman, D R., Sheppard J J and Karpman H L Diagnosis of occult arrhythmias by Holter electrocardiography Prog Cardiovasc Dis. **16** 569 1974
4 Jervell A., and Lange-Nelson F Congenital deaf mutism functional heart disease with prolongation of the QT interval and sudden death, AM HEART J **89** 378 1975
5 Schwartz P J., Perite M., and Malliane A The long Q T syndrome AM HEART J **89** 378 1975
6. Reynolds, E W and Vanderark C R. Quinidine syncope and the delayed repolarization syndromes, Mod Conc Cardiovasc Dis **45** 117 1976
7 Schwartz P J and Wolf S QT interval prolongation as predictor of sudden death in patients with myocardial infarction Circulation **57** 1074 1978
8 Haynes, R. E., Hallstron A P., and Cobb L. A. Repolarization abnormalities in survivors of out-of hospital ventricular fibrillation Circulation **57** 654 1978
9 Engel T R., Meister S G and Frankl, W S The R on T phenomenon Ann Intern. Med. **88** 221 1978
10 DeSoyza N Bissett J K Kane J J., Murphy M L., and Doherty J E Ectopic ventricular prematurity and its relationship to ventricular tachycardia in acute myocardial infarction in man, Circulation **50** 529 1974
11 Rothfield E L. Parsonnet J., McGorman W., and Linden S Harbingers of paroxysmal ventricular tachycardia in acute myocardial infarction, Chest **71** 142, 1977
12. Wellens H J J Duren D R., and Lie K I Observation on mechanisms of ventricular tachycardia in man Circulation **54** 237 1976
13. Josephson M E Horowitz L N., and Farshidi, A Continuous local electrical activity a mechanism of recurrent ventricular tachycardia Circulation **57** 659 1978
14 Han J and Moe G K Nonuniform recovery of excitability in ventricular muscle Circulation **14** 44 1964
15 Leahey E B Reiffel J A., Drusin R. E Heissenbuttel, R H Lovejoy W P., and Bigger J T Interaction between quinidine and digoxin J.A.M.A **240** 533 1978.
16 Hoffman B F Rosen M R and Wit A L. Electrophysiology and pharmacology of cardiac arrhythmias. VII Cardiac effects of quinidine and procaine amide. AM. HEART J **90** 117 1975
17 Anderson J L. and Mason J W Successful treatment by overdrive pacing of recurrent quinidine syncope due to ventricular tachycardia Am J Med. **64** 715 1978
18 Shub C Gau G T., Sidell, P M., and Bennan L. A. The management of acute quinidine intoxication, Chest **73** 173 1978

Spontaneous cure of infected left atrial myxoma following embolization

Marc J Schweiger M D
Jesse G Hafer, Jr , M D
Richard Brown M D
Ralph E Gianelly M D
Springfield Mass

The symptoms of cardiac myxoma are varied Prior to the advent of echocardiography diagnosis was most difficult requiring a high degree of clinical suspicion We describe a patient with three unusual clinical events prolonged duration infected atrial myxoma and disappearance of the echocardiographic findings of myxoma following embolization

Case report

The patient J M is a 51 year-old white female who was admitted [illegible] the Baystate Medical Center hospital on August [illegible]1 19[illegible] [illegible] awakening at night with a severe headache Disorientation and inability to walk were noted. She had been entirely well until 1[illegible] years prior to admission when she sustained a cerebrovascular accident presumed to be embolic At that time she had been unconscious for one week It was felt that her embolus was secondary to rheumatic heart disease and the patient was treated with coumadin which was administered continuously until her admission in August 1977 No definite history of rheumatic fever was obtained. In the few months prior to this admission the patient had experienced excessive uterine bleeding a D & C was performed one month prior to admission In addition, a few months prior to admission the patient had visited the dentist to have her teeth cleaned She did not receive endocarditis prophylaxis for either procedure Over the few months prior to admission the patient complained of increasing fatigue Physical examination on admission to the hospital revealed a temperature of 101 F Her eyes were fixed and deviated to the right She had vertical nystagmus upon lateral gaze The fundoscopic examination was normal and her neck was stiff A computerized axial tomographic scan was performed which revealed a left cerebellar hemorrhage as well as an old left parietal infa[illegible] with surrounding secondary atrophic changes. Her hem[illegible] on admission was 26 and her white blood count was 9,0[illegible] a normal differential Routine laboratory data were all [illegible] normal limits The electrocardiogram on admission reve[illegible] sinus tachycardia but was otherwise normal. Ches[illegible] x ra[illegible] normal. On August 23 suboccipital craniotomy and dra[illegible] of a posterior fossa hematoma was performed. The ma[illegible] sent to pathology was reported as showing red thromb[illegible] patient gradually recovered from her neurological de[illegible] Three blood cultures drawn on admission, prior to sur[illegible] subsequently yielded *Streptococcus viridans* The diagno[illegible] subacute bacterial endocarditis was made and the patient [illegible] begun on intravenous penicillin therapy On September [illegible] echocardiogram was performed which showed multiple ec[illegible] behind the anterior leaflet of the mitral valve in diastole [illegible] 1A) This was felt to be most consistent with a left a[illegible] myxoma, although the possibility of a thrombus or vege[illegible] could not be ruled out with certainty Cardiology consulta[illegible] was obtained and examination revealed a loud first h[illegible] sound, a physiologically split second sound, and a grade [illegible] II/VI early systolic murmur at the apex. There was no sou[illegible] in diastole The rest of her physical examination was enti[illegible] within normal limits It was felt that following the pati[illegible] course of penicillin therapy an angiographic evaluation of [illegible] left atrium should be made Repeat echocardiogr[illegible] performed on September 10 and September 21 showed [illegible] significant change from the original echocardiogram. [illegible] October 11 while the patient was awaiting cardiac cathet[illegible] zation she experienced sudden pain and numbness in b[illegible] legs. There were absent femoral and distal pulses bilaterally [illegible] diagnosis of an aortic saddle embolus was made. She [illegible] immediately brought to the operating room where a laparo[illegible] my was performed to remove the embolus Patholog[illegible] examination of the embolus revealed "a heterogene[illegible] mixture of material with characteristic features of myxo[illegible] tumor of the type found in the heart There were mul[illegible] islands of single and multinucleated cells with hypochro[illegible] nucleae These cells are surrounded by pools of mucopol[illegible] charide material. Primitive capillaries in cords of cells [illegible] seen" (Fig 2A) Bacterial colonies were noted within and [illegible] the surface consistent with active infection (Fig 2B). [illegible] October 14 a repeat echocardiogram was performed which [illegible]

From the Department of Cardiology and the Department of Medicine Baystate Medical Center Springfield Mass

Received for publication Dec 19 1978

Accepted for publication Feb 14 1979

Reprint requests Marc J Schweiger M D Dept of Cardiology and Dept. of Medicine Baystate Medical Cente[illegible] [illegible] Chestnut St Springfield, Mass. 01107

Fig 1A Echocardiogram at the level of the mitral valve A cloud of echoes is apparent behind the anterior leaflet of the valve *The two dark lines* present were drawn to aid in making calculations.

Fig 1B Echocardiogram demonstrating the absence of echoes behind the anterior leaflet of the mitral valve area

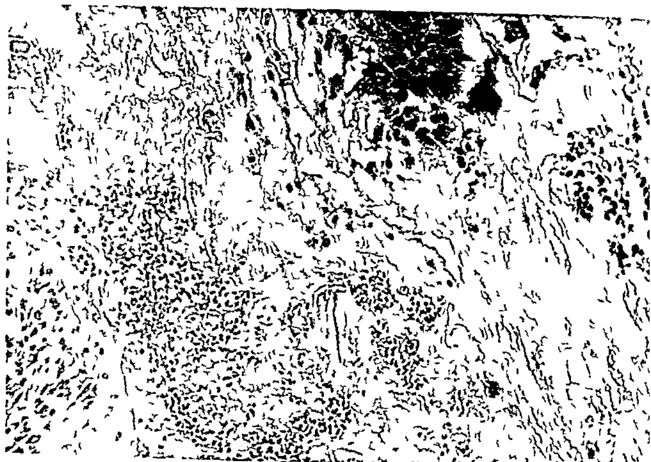


Fig 2A Pathology slide of material removed at laparotomy There are multiple islands of single and multinucleated cells with hypochromic nucleae The cells are surrounded by pools of mucopolysaccharide material Primitive capillaries are seen (Hematoxylin and eosin ×250)

entirely within normal limits (Fig 1B) There were no echoes apparent behind the anterior leaflet of the mitral valve On October 19 a right sided catheterization with pulmonary arteriogram and left sided follow through was performed There was no evidence of mass in the left atrium Multiple repeat blood cultures were negative The patient remained asymptomatic on no therapy and was discharged from the hospital November 1 1977 in good condition with no symptoms referable to her cerebellar hemorrhage or saddle embolus Her most recent evaluation eight months after discharge was unremarkable Repeat echocardiogram showed no evidence of myxoma

Discussion

Our patient had done extremely well following a cerebral embolus 15 years previously Since she does not have valvular heart disease nor any other known predisposing factors towards premature cerebrovascular disease it seems likely that her original cerebrovascular accident was secondary to emboli from the myxoma Most reports indicate that left atrial myxoma is associated with progression of symptoms within two to three years[1] However Goodwin[1] had one patient i his series with symptoms for 15 years Aldrid and Greenwood in their series of 31 patients wit myxoma described one patient with sympto for 20 years Levine[3] discussed a patient with right atrial myxoma which presumably had bee present for 28 years Our patient as well appea to have had her left atrial myxoma for prolonged period of time

There have been five previous reports o infected atrial myxoma documented by positiv blood cultures and organisms in the myxoma Only three of these were diagnosed antemortem and only two patients survived Four patients sustained cerebral emboli In three of the patient the embolic episodes were associated with the infection although this was the immediate cause of death in only one One patient had *Staphylococcus aureus* bacteremia which was treated with antibiotics and developed a superinfection[7] with *Candida parapsilosis* which was cultured

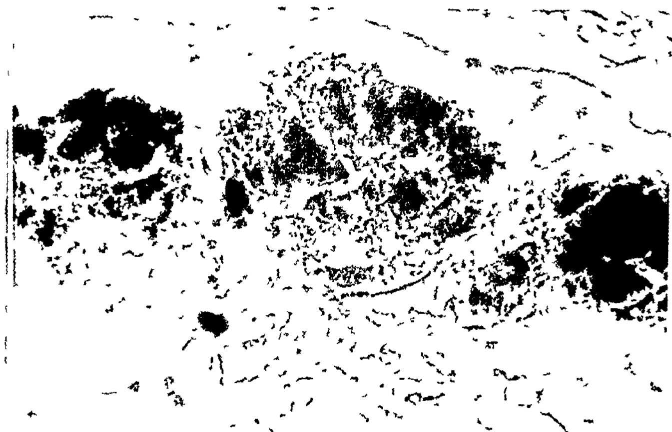


Fig 28 Bacterial colonies noted on the surface of the myxoma (Hematoxylin and eosin original magnification ×420)

from the blood and from the myxoma at postmortem The second patient developed *Streptococcus faecalis* bacteremia and died from a mesenteric embolus two weeks after sustaining a cerebral embolus[5] A third patient had been admitted to the hospital with fever and confusion Blood cultures yielded *Staphylococcus aureus* and an echocardiogram showed a left atrial myxoma This patient sustained a cerebral embolus and died The first reported surviving patient was a 50 year old female who was admitted with fever and disorientation Three blood cultures were positive for *Staphylococcus albus* and one for *Streptococcus viridans* On physical examination she had signs suggestive of cerebral emboli as well as an intermittent diastolic murmur The levo phase of pulmonary angiography demonstrated a pedunculated mass moving between the atrium and ventricle Because of the recent embolic episode it was felt that immediate surgery was indicated despite the bacteremia An atrial myxoma was removed and *Streptococcus viridans* was cultured from the myxoma The patient was alive and well 8 months after surgery[7] Recently a 48 year old woman had an atrial myxoma removed surgically and was found to have hyphal forms typical of *Histoplasma capsulatum* on a thrombus superimposed on the myxoma Fungal cultures of bone marrow blood and pericardial fluid grew *Histoplasma capsulatum* The patient was subsequently treated with amphotericin B and steroids and was discharged 60 days following surgery Thus including our patient there have been six cases of infection associated with a left atrial myxoma Four of the six had embolic episodes associated with the active infection Three of the six survived two following surgery during the active stage of infection and our patient after successful removal of the saddle embolus

Embolic complications of myxomas are common ranging from 33% to 48% in three large series[1,3,4] Although the embolic material generally consists of tumor fragments or thrombus

from the tumor surface large emboli have been reported [9,11] Selzer and associates[10] discussed the case of a 51 year old woman with a murmur of mitral stenosis which disappeared following aortic saddle embolus Eighteen months later congestive symptoms occurred and a diastolic murmur was again heard Angiography showed a left atrial mass and the myxoma was subsequently removed surgically Carter and colleagues[11] described a 60 year old female who sustained an aortic saddle embolus The material removed surgically was a typical myxoma The patient had no diastolic murmur and an angiogram via an antecubital vein demonstrated no filling defect

Both echocardiography and the levophase of pulmonary angiography in our patient demonstrated no mass although a small fragment of residual stalk would not be detected by these tests It is conceivable that her infection caused the severance of the stalk of the myxoma and it is certainly possible that a residual portion of the stalk was retained Most myxomas arise from the atrial septum near the fossa ovalis and are pedunculated The other known survivors of an infected myxoma had the myxoma removed during the ac i e stage of infection Therefore it seems adv s k to recommend surgery despite active inf ct n in an attempt to prevent a catastrophic embolization Our patient sustained such an embolus after consideration of surgery had been postponed until the active course of antibiotic therapy for endocarditis could be complete Fortunately she recovered Since atrial myxomas are known to recur after surgery [9] and in spite of the possibility of residual myxoma we have decided to follow our patient with serial examinations and echocardiograms

We have shown the sequential disappearance demonstrated echocardiographically of a left atrial myxoma Certainly all patients with or without bacteremia who systematically embolize without predisposing factors deserve echocardiography Additionally a negative echocardiogram does not rule out the previous presence of the myxoma and in certain situations for example unexplained embolization repeat echocardiog phy is probably indicated

Summary

A patient with prolonged duration bacte infection and echocardiographic disappeara of an atrial myxoma following embolization discussed Following aortic saddle embolus, echocardiographic manifestations of the patie left atrial myxoma disappeared Previous case infected atrial myxomas are reviewed The nec sity of early surgical intervention despite act infection is discussed

We would like to thank Dr Hugh McAllister and colleagues at the Armed Forces Institute of Pathology their pathological analysis Dr Nori Shiraki for his hel preparing the photomicrographs and Ms Henrica Maas her help in preparation of the manuscript We would also to thank Dr Paul Friedman for his expertise in surg removing the embolic material

REFERENCES

1 Goodwin J F Diagnosis of left atrial myxoma La 1 464 1963
2 Aldridge H E and Greenwood W F Myxoma of left atrium Br Heart J 22 189 1960
3 Case records of the Massachusetts General Hos (Case 48 1970) N Engl J Med 283 1157 19 0
4 Dick H J and Mullin E W Myxoma of h complicated by bloodstream infection by *Staphyloco aureus* and *Candida parapsilosis* N Y State J M 56 856 1956
5 Rae A Two patients with cardiac myxoma—one senting as bacterial endocarditis and one as conge heart failure PostGrad Med J 41 644 1965
6 Graham H V Vonhartzsch B and Medina J Infected atrial myxoma Am J Cardiol 38 658 19
7 Malloch C I Abbott J A and Rapaport E Le myxoma with bacteremia Am J Cardi l 25 3 3 1
8 Rogers E W Weyman A E Noble R J and Bru S C Left atrial myxoma infected with *Hist plas capsulatum* Am J Med 64 683 1978
9 Greenwood W F Profile of atrial myxoma Am Cardiol 21 367 1968
10 Selzer A Sakai F J and Popper R W Prot clinical manifestations of primary tumors of the he Am J Med 52 9 1972
11 Carter A B Loge K G and Hill I G W Card myxoma in aortic saddle embolism Br Heart J 22 1960
12 Jugdutt B I Rossall R E and Stearns L P unusual case of recurrent left atrial myxoma Can M Assoc J 12 1099 1975

Rheumatic fever in children

Germano DiSciascio M D
Angelo Taranta M D
New York N Y and Valhalla N Y

Eva Eva with rising fever
What does your work up show?
Is there arthritis?
A touch of St Vitus?
How high is your ASO?
The sounds I hear I fear my dear
Mark regurgitant flow
But Jones criteria
Have yet to appear in ya
So you re still an F U O
Anonymous Medical Student 1964

Is rheumatic fever worth the trouble? For almost four decades now we have been offered a steady diet of obituary notices of this disease If one looks at the widely quoted Danish data (Fig 1) the first impression is that the rheumatic fever incidence has been falling so precipitously that it must surely have gone through the floor by now

But most children don t live in Denmark In fact four fifths of the children living today are said to be living in the poverty stricken Third World The news we get from there are fragmentary at best but the impression is that of a *déjà vu* with Cairo and Lima reenacting the rheumatic fever scene of Boston and New York in the 1920 s It is not therefore only out of a perverse love of the esoteric and the untimely that we present this review of rheumatic fever in children

Epidemiology

The decreasing incidence of rheumatic fever (RF) and rheumatic heart disease (RHD) in the so called Western world (which includes of course Japan) has become an axiom which meets the consensus of the pediatrician the cardiologist and the epidemiologist The number of hospitalized cases of RF is declining the disease is becoming milder the Jones criteria have been made more exacting and the identification of non rheumatic cardiac diseases mimicking RHD has become more frequent Migrations urbanization industrialization and the advent of antibiotics have changed the environment and the host and thereby altered the natural (or perhaps now unnatural?) history of the disease

Morbidity and mortality In Scandinavian countries the reported incidence of RF has dropped drastically over a century from 200 to 11/100 000 (see Fig 1) In the U S the annual incidence of RF in Connecticut hospitals decreased from 12 3 in the period 1934 1938 to 2 9/100 000 in the period 1968 1972[2] and in Nashville from 14 9 in 1964 to 6 4/100 000 in 1969[3] The annual rate in Baltimore decreased from 40 in 1935 to 23/100 000 in the period 1960-1964 in the age group 5 to 19 interestingly the decline was accounted for mainly by a decrease of recurrences (Fig 2)

A look at the crude death rates from RF and RHD in the U S shows a reduction from 14 5 to 6 8/100 000 in the period 1950 to 1972[5] The age specific death rates indicate that the greatest decline occurred among the young who may have benefited the most from the advent of antibiotics (see Table I)

Medical care as an environmental factor Among the changing environmental factors is the availability of medical care In the districts of Baltimore serviced by comprehensive care programs (children and youth programs) the incidence of RF declined 60% while it remained

From th Department of Med cin Cabrini Medical Cent New York, N Y and the Division of Rheumat l gy and Immun logy Depart ment of Medicine New Y k Medical Coll g Valhalla, N Y
Rece ed fo publication Dec 29 19 8
Reprint requests Angelo Taranta M D Cabrini Medical Center Dept. of Med in 2?7 E Nineteenth St New York N Y 10003

000? 8 03/80/050635 + 2450? 40/0 © 1980 The C V Mosby Co



Fig 1 Decline in rheumatic fever incidence in Denmark 1862 to 1962 Redrawn as semi log plot from Vendsborg P Faverholdt L and Olesen K H Decreasing incidence of a history of acute rheumatic fever in chronic rheumatic heart disease Cardiologia 53 332 1968 Reproduced with permission

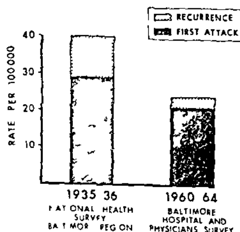


Fig 2 Decline of the incidence of rheumatic fever in the Baltimore hospitals From Markowitz and Gordis Rheumatic Fever p 7 Philadelphia 19?? W B Saunders Company Reproduced by permission

unchanged or increased in the rest of the city The decline occurred only among the subpopulation of patients with previous sore throat which is the signal for initiating antistreptococcal therapy and not in the other subset of rheumatic fever patients who had no sore throat prior to the rheumatic fever attack and therefore could not have been helped by the availability of care (see Fig 3) Thus whether medical care is available

Table I Age specific death rates from rheum[...] fever and rheumatic heart disease in the U S

Age group (yr)	*Deaths per 100 000*		*Decline (%)*
	1950	*1972*	
<24	2 81	0 25	91
25-44	11 35	2 71	[illegible]
45 64	27.53	13 92	50
>64	54 53	31 48	4[illegible]

From Mortimer E A Control of rheumatic fever-How are we d[...] (Editorial) J.A.M.A 237 1720 1977 Reproduced with permissio[n]

and accessible makes indeed a difference

Changes independent of medical care On [the] other hand rheumatic fever started to decl[ine] before the introduction of antibiotics (see ag[ain] Fig 1) Other factors are believed to have play[ed a] role such as improved socioeconomical con[ditions] and especially housing (less crowding) [In] the U S A living space has been increasing stea[dily] even among the poor until recently althou[gh] from 1974 to 1976 apartments have been gett[ing] smaller (6½ square feet nationwide) and m[ore] people have been living in apartments

Streptococcal changes The decline in RF in[ci]dence may also be explained with a change in [...]

streptococci themselves Quinn and Federspiel[9] demonstrated a decrease in the percentage of Group A streptococci among the beta hemolytic streptococci isolated from the throat of Nashville children from 84% in the period 1953 to 55 to 62 6% in the period 1961 to 67 and a drop in the percentage of typable strains among the Group A streptococci from 51 2% to 17% in the same period (but this could be due to the advent of new M types for which no typing sera were available [8])

By contrast evolutionary changes in the streptococcus and/or human immunity can be responsible for increased incidence of RF as in the Ryukyu Islands where an outbreak of the disease occurred in 1973 the year of their reversion from U S.A to Japan This political change brought in tourism and with it new dominant serotypes to which the natives were not immune [9]

Rheumatic fever in developing countries Exposure of immigrants to unfamiliar serotypes rampant urbanization and rapid increase in schools might explain the apparently increasing incidence of RF in many developing countries * Another fraction of this increase may be artifactual and due to increased awareness of the disease less competition for attention from decreasing communicable diseases and more attention to the health of the natives after independence or during the struggle for it Thus progress has many components with different in fact often opposite effects on rheumatic fever incidence (Fig 4)

Typical of these developing localities is Soweto the black township on the outskirts of Johannesburg where a careful recent epidemiologic study revealed a prevalence rate of RHD among school children of 6 9/1 000 with a peak rate of 19 2 per 1 000 children in the seventh grade one of the highest recorded reliably in recent times [10] The highest reported mortality rate in the world for RHD (27 5/100 000) and one of the highest for ARF (1 0/100 000) are in Egypt whose capital lodges ¼ of the total country population in conditions of extreme crowding and where rheumatic fever is frequent By contrast in the Egyptian countryside rheumatic fever is comparatively rare despite the prevailing poverty [1]

Dev l ping is a wishful thinking kind of word as many d l ping co ntries are devel p ng imperceptibly We prefer the term po r which is what is usually m ant but use the tw terms int hange bly

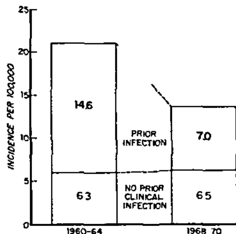


Fig 3 Declining incidence of first attack of rheumatic fever in patients with previous sore throat From Gordis L. Effectiveness of comprehensive care programs in preventing rheumatic fever N Engl J Med 289 331 1973

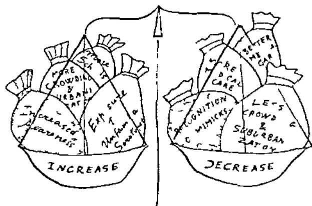


Fig 4 Factors affecting the incidence of rheumatic fever in the western world and "developing" countries

Rheumatic heart disease and juvenile mitral stenosis in developing countries Rheumatic heart disease is the most common form of heart disease in tropical countries in Bangkok it affects 39% of all patients hospitalized for heart disease [12] and a recent review in Thailand reports a very high incidence of carditis and of juvenile tight mitral stenosis the latter attributed to the early onset of subclinical chronic valvulitis or to the frequency of recurrences in the young age group or to both [1] A high incidence of rheumatic fever at a very young age has been reported in other tropical countries D Arbela and colleagues [3] found a peak incidence of the disease in the 6 to 10 year age group followed by the 11 to 15 year age

group with 10% of the total cases in the 0 to 5 year age group (in Kampala, Uganda) This finding is consistent with the higher ASO levels in young children reported from the same hospital [13] Similar data were collected in East Nigeria in Khartoum and in Pakistan indicating earlier exposure to *streptococci and* earlier occurrence of post streptococcal diseases in these *regions* [14]

Is juvenile mitral stenosis a true variant of rheumatic heart disease? If so is it a variant occurring specifically in *tropical* or underdeveloped countries? The answer to both these questions remains moot The data *purporting* to show a difference in the incidence of tight mitral stenosis in the young are hospital statistics with an uncertain denominator Moreover in *some series* it is not clear whether mitral regurgitation is separated from mitral stenosis and whether congenital lesions are distinct from rheumatic [15] And certainly in a population where most people are very young as is true in *many* tropical and developing countries the chances of observing diseases in children by *necessity* increase So does the chance of observing a rare manifestation of such diseases However to the best of our knowledge tight mitral stenosis was never a common lesion in children in the Western world even when rheumatic fever was rampant Only 1 3% of 1 000 commissurotomies reported by a New York surgeon in [illegible] were on patients under 20 [16] By contrast 34[illegible] of [illegible]73 commissurotomies reported by a Vellore South Indian group in 1964[17] were on patients of the same age and similar reports abound

It is often stated that only 50% of the patients with premature mitral stenosis have Aschoff bodies at surgery or autopsy It is also reported that only one third to one half of these children have a history of rheumatic fever and that this history is often atypical How do these clinical findings correlate with the pathologic ones? Can one identify through this correlation a cluster of rheumatic and another cluster of non rheumatic patients? (Similar questions can be asked of mature mitral stenosis in the West) Obviously a lot remains to be learned and almost everything remains to be explained about this obscure and important disease

Biologic aspects

Conventional wisdom holds that rheumatic fever if it is a problem at all is a problem of

technology rather than science of dev[...] rather than research applied not bas[...] not biologic A fresh look at the evid[...] persuade the reader that rheumatic feve[...] fully understood as it is often thought [...]

Surface structure of the streptoco[...] The surface components of pathogenic [...]ganisms in general and of group A strept[...] particular have been the object of [...] investigative attention These compone[...] stick to the host's mucosal cells if an [...] beachhead is to be established they [...] antigenic determinants that must be re[...] as foreign and they should be hard to [...] phagocytosis is to be resisted

Which are the structures that underl[...] functions? Going from the outside in we [...] may not find a capsule of hyaluronic aci[...] frequent in epidemic strains) [18] *Since* [...]coccal hyaluronic acid is identical with [...] human connective tissues it cannot be rec[...] as foreign and therefore does not elicit an [...]dy response Probably because of its slim[...]pery quality the hyaluronic acid capsule h[...] phagocytosis Under the capsule if one [...] may or may not be found fimbriae non [...] flagella which correlate with virulence [19] [...] fimbriae rest two substances lipoteichoi[...] and M protein each favoring virulence in [...] fashion

Lipoteichoic acid sticks to epithelial [...] Exposing epithelial cells from the human [...] mucosa to lipoteichoic acid in solution im[...] later attachment of streptococci presu[...] because binding sites or receptors on the su[...] of the epithelial cells become saturated wit[...] lipoteichoic acid in solution and therefore ca[...] bind any more with the lipoteichoic acid o[...] fimbriae [20]

The other virulence factor located in fimbr[...] M protein or better the M proteins wh[...] form the basis for the prevailing system of cla[...]cation of group A streptococci *into types* [...] proteins interfere with phagocytosis and [...] bodies against them overcome *the interfere*[...] Because there are more than *60 M prote*[...] usually one in each virulent strain the immu[...] to streptococcal infections is limited to mem[...] of the same type sharing the same M prot[...] though a few exceptions are known

Stimulated largely by the hope *of develop*[...] an antistreptococcal vaccine much work [...]

able II Cross reactions between streptococci and human tissues

Streptococcal component	*Human component*	*Authors (year)*
like protein in cell wall of some group A strains	Myocardium	Kaplan & Meyserian (1962)
Glycoprotein of cell membrane	Glycoprotein of glomerular basement membrane	Markowitz & Lange (1964)[19]
Antigen of cell membrane	Histocompatibility antigen	Rapaport (1966)
l membrane of all group A strains	Myocardial sarcolemma?	Zabriskie & Freimer (1966)
ype I streptococcal cells	Myocardial intercalated discs	Lyampert (1966a)
our distinct antigens in acid extracts of streptococcal cells	Four distinct myocardial antigens	Lyampert (1966b)[11]
Group A polysaccharide	Glycoproteins of heart valves	Goldstein (1967)
Three distinct streptococcal antigens	Three distinct kidney antigens	Holm (1967)
Streptococcal hyaluronic acid	Mammalian hyaluronic acid and protein polysaccharide	Sandson (1968)[14]
Type I M protein	Several H LA antigens	Hirata & Terasaki (1970)
Antigen of cell membrane	*Neuronal cytoplasm of caudate and subthalamic nuclei*	Husby (1976)

been done on M proteins several of which have been purified. Up to recently even highly purified M protein preparations were associated with a non type specific determinant[22] responsible for delayed hypersensitivity responses Serum antibody to this non type specific M associated antigen or protein is common in human sera Fortunately brief digestion with pepsin greatly reduces the non type specific determinants and isoelectric focusing of an alkaline extract of M protein may have a similar effect[23]

The term M associated protein (MAP) is used by some authors to identify what others call non type specific protein MAP is present only in strains containing M protein three varieties have been described by immunologic and electrofocusing techniques,[24] and high anti MAP titers have been reported in sera of rheumatic fever patients[25] In addition a type specific serum opacity factor (SOF) has been found in close association with M protein[26] M protein and SOF appear to be controlled by closely associated genes located in extrachromosomal plasmid(s) or bacteriophage

The rigid exoskeleton of the streptococcal cell—the cell wall—is made of group A carbohydrate (rhamnose and N acetylglucosamine) and peptidoglycan While the streptococcal exoskeleton is similar to the rigid cell walls of plant cells the soft cytoplasmic membrane underlying it is similar to the cytoplasmic membrane of mammalian cells It contains an antigen cross reactive with human sarcolemmal membrane of which more in the next section

Immunologic cross reactions between streptococcal and human antigens Immunological similarities between mammalian hosts and microbial parasites are important from at least two standpoints They may trick the host into recognizing the microorganisms erroneously as self the immune response will then be blunted or abolished[27] They may also elicit the formation of antibodies directed against the microbial products but capable of reacting with some of the host s antigens as well Immunologically mediated tissue damage may result

Many immunologic cross reactions have been described between antigens of group A streptococci and those of man (Table II) Which one if any is a mediator of tissue damage remains uncertain

Among the cross reactive antibodies those against the cell wall polysaccharide of group A streptococci are of special interest because they have been reported to cross react with structural glycoproteins of human heart valves[3] a critical structure in rheumatic heart disease and also to persist in patients with residual valvular disease but not in those without it[39] This difference however could not be confirmed in a large series of patients studied with a different method (quantative precipitation in gel rather

Table III Rheumatic fever in 56 twin pairs*

	Concordant pairs	Discordant pairs	Concordance rate (per cent)
16 Monozygotic twin pairs	3 (4)†	13 (12)†	18 7 (25)†
40 Dizygotic pairs	1 (2)†	39 (38)†	2 5 (5)†

Based on data of Taranta, A Torosdag S Metrakos J Jegier W and Uchida I. Rheumatic fever in monozygotic and dizygotic twins Proceedings of the Tenth International Congress of Rheumatology Minerva Medica Torino 1961 pp 96-99 Reproduced by permission
†Taking into account pairs of questionable concordance

Table IV Clinical manifestations of rheumatic fever in members of definitely and questionably concordant twin pairs*

	Monozygotic twins								Dizygotic twins			
	1		2		3§		4†		1		2†	
	A	B	A	B	A	B	A	B	A	B	A	B
Arthritis or arthralgia	+	+	+	+	+	+	+	+	+	+	−	−
Carditis	+	+	+	+	+	+	−	−	+	+	−	+
Chorea	−	−	−	−	−	−	−	−	−	−	+	−
Erythema marginatum	−	−	−	−	−	−	−	−	+	−	−	−

Data of Taranta A Torosdag, S Metrakos J Jegier W, and Uchida I Rheumatic fever in monozygotic and dizygotic twins Proceedings of the Tenth International Congress of Rheumatology Minerva Medica, Torino 1961, pp 96-99 Reproduced by permission
†Questionably concordant
§Concordant also for the rare sequel, juvenile mitral stenosis

radioimmunoassay) [9] and in subsequent studies with the radioimmunoassay technique the level of group A antibody decreased after valvectomy suggesting that the cause of the sustained antibody response in patients with rheumatic heart disease if it does indeed occur may be the cross reacting valvular tissue itself [9]

The nature of the group A streptococcal membrane antigen cross-reactive with human heart was reinvestigated recently by absorption of rheumatic fever sera with sarcolemmal sheets and subsequent elution The antibody so purified was used to follow the purification of the streptococcal membrane antigen which turned out to consist of four distinct polypeptides with molecular weights ranging from 32 000 to 22 000 daltons [4]

Attempts to demonstrate a state of delayed hypersensitivity against heart antigens in pa

Table V Estimated relative odds of con
of rheumatic manifestations and cardia
lae*

Manifestations	Estimated relative	
	Not adjusted	Adju age c and
Joint involvement	4.82	
Carditis	1 44	
Chorea	†	4
Heart disease	2.34	

From Spagnuolo M and Taranta A Similarity in
manifestations of rheumatic fever in siblings, N Engl J M
1968 Reproduced by permission
†The data presented for chorea were already adjusted fo

tients with rheumatic fever have yielded
results [43] In the guinea pig however sens
to group A streptococcal antigens result
acquisition by T lymphocytes of the abil
guinea pig myocardial cells in vitro

Streptococci associated with phary
with impetigo relation of serologic
specific streptococcal sequels Nature
be wanting to tell us something by lett
matic fever occur after streptococcal infe
the throat but not of the skin The m
ambiguous however since streptococc
tions of the skin and those of the throat
more than one respect Not only is the an
site different but so are the predomin
logic types (roughly the first 48 M t
pharyngitis types and types with higher
are skin types) and the immunologic
they elicit (lower antistreptolysin respo
skin infections) [45]

Some authors have postulated that the
geal site may be the critical factor in the
events leading to rheumatic fever be
peculiarities of the lymphatic drainag
throat others that the cutaneous site
critical as an interruption of that chai
inhibition of streptolysin O by skin lipid

Bisno and co workers[47] have pointed
acute rheumatic fever does not occur in M
Tennessee during the summer when p
types prevail in throat cultures It is
however whether these skin types which
ly colonize the throat actually in
Recent evidence from Trinidad indica
pyodermal strains when in the throat
associated with rheumatic fever

Whether all the pharyngeal strains carry the same risk of eliciting rheumatic fever is also uncertain Rammelkamp s observations[49] indicated a constant risk of approximately 3% which didn t vary from year to year or from strain to strain as long as the strain was capable of causing a definite pharyngitis But Kuttner and Krumwiede[50] reported that a virulent epidemic of type 4 streptococcal pharyngitis among children with previous rheumatic fever failed completely to elicit recurrences and Widdowson and associates[51] recently presented evidence that production of lipoproteinase opacity factor may be associated with diminished rheumatogenicity On the basis of these and other observations Stollerman[52] has argued that there are rheumatogenic and non rheumatogenic strains in analogy with the well established distinction of nephritogenic and non nephritogenic strains

Immunogenetics If the detailed study of the microorganism fails to reveal why some patients with streptococcal infections develop rheumatic fever and most don t then a detailed study of the host perhaps will Monozygotic twins have a higher concordance rate for rheumatic fever than dizygotic twins (Table III) and their clinical manifestations are more concordant also (Table IV)[53] Even in siblings other than twins the similarity of clinical manifestations of rheumatic fever is significantly *greater than it would be* accounted by chance alone (Table V)[4] All these observations intimate that a host factor probably genetic contributes to determine whether after a streptococcal infection rheumatic fever will appear in any given individual

Efforts to find a marker for this postulated susceptibility have failed thus far HLA types which correlate with the susceptibility to many diseases don t seem to correlate consistently with the susceptibility to rheumatic fever[55, 5] Nevertheless the intriguing observations of an association of immune responsiveness to streptococcal antigens and HLA type[57] and of decreased mixed lymphocyte reactions among rheumatic subjects[58] suggest the potential fertility of the immunogenetic approach *

Note add d in proof A novel B cell ll ntigen provisionally named 883 has n w been reported in association w th heum tic feve in two distinct populations f pat ents and with a relati e risk of 12 9 (Patarroyo M Winchester R. Vehera o A Cabof ky A., Ch lem F Zabriskie J B and Kunk l, H G Assoc at on of a particul r B cell allo tigen with suscept bility to heumatic fe r F rty third An ual Meet g f the Am n an Rheumat sm Associat n M y 30-June 1 1979)

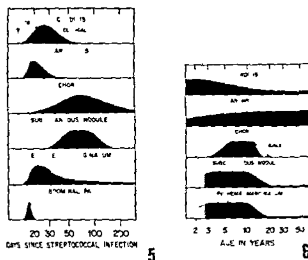


Fig 5 Schematic diagram of the sequ nce of appearance of the various rheumatic fever manifestations The maximum height of each curve indicates the time at which most of the cases of a given manifestation appear " i e become known to a medical observer Due to the concentration of events early in the attack, time is represented on a logarithmic scale From Taranta A Clinical aspects of rheumatic fever *in* Arthritis and Allied Conditions 9th ed J L Hollander and D J McCarty Jr editors Philadelphia 1979 Lea & Febi er Reproduced by permission

Fig 6 Schematic diagram of the variations with age of the incidence of the major manifestations of rheumatic fever The maximum height of each curve indicates the age of maximum incidence From Taranta A Clinical aspects of rheumatic fever *in* Arthritis and Allied Conditions 9th ed J L Hollander and D J McCarty Jr editors Philadelphia 1979 Lea & Febiger Reproduced by permission

Clinical manifestations

Although arthritis is emphasized in its name RF is not important because of it since arthritis is short lived and leaves no sequel with one questionable exception (see below) Carditis is the most serious manifestation because it is the only one that can cause death during the acute attack residual disability and late mortality

The incidence of the reported clinical manifestations of RF varies according to the age and sex of the patient the diagnostic criteria used and the time and place in which the series were collected Yet series of *first attacks* studied prospectively and carefully are remarkably similar throughout the world[5, 60] Recurrences differ in having more frequent and more severe carditis and higher mortality Many of the differences among RF series stem probably from varying proportions of recurrences to first attacks

Fig 5 shows the sequence of the appearance of the manifestations and Fig 6 the variations



Fig 7 Erythema marginatum (Courtesy of Dr B F Massell Boston, Mass)

Table VI Jones criteria (revised) for guidance in the diagnosis of rheumatic fever*

Major manifestations	Minor manifestations	
	Clinical	*Laboratory*
Carditis Polyarthritis Chorea	Previous rheumatic fever or rheumatic heart disease	Acute phase reactions Erythrocyte sedimentation rate
Erythema marginatum	Arthralgia	C reactive protein leukocytosis
Subcutaneous nodules	Fever	Prolonged P R interval

Supporting evidence of streptococcal infection
Increased titer of streptococcal antibodies
ASO (antistreptolysin O)
Other antibodies
Positive throat culture for Group A streptococcus
Recent scarlet fever

From Stollerman G H Markowitz M Taranta A Wannamaker L W and Wittemore R Jones Criteria (revised) for guidance in the diagnosis of rheumatic fever Circulation 32 664 1965

with age Arthritis becomes increasingly frequent with age while carditis has an opposite trend

Arthritis is exquisitely painful Joints predominantly the large ones and especially of the lower limbs are affected in quick succession each joint maximally for only a few days or a week at the most so that the arthritis of several joints overlap partly in time

If arthritis is not shortened by antiinflammatory treatment it can last 1 week or in ⅓ of the cases 2 to 3 weeks Arthritis tends to be of shor duration and to be less severe in children than adults[61]

The arthritis of rheumatic fever has b reported to last longer in Scandinavian count (up to 1 year)[6] which we find puzzling radiologic joint changes other than soft tis swelling are ever found in rheumatic fever after it, with the questionable exception *Jaccoud s arthritis* This is characterized deformities of the fingers with erosions of metacarpal heads resulting in characteri hook like deformities[63 64] Jaccoud arthritis if indeed a sequel of rheumatic fever is an extre ly rare one

Carditis is diagnosed by characteristic aus tatory signs such as the apical systolic murmu mitral regurgitation which is characteristic long occupying most or all of systole (holo tolic), blowing, of relatively high pitch and wi loudness of at least two but usually three more on a scale of six (a corollary of its loud is that it can be heard in the axilla and is obliterated by inspiration or changes in postu the apical mid diastolic murmur (Carey Coom presumedly due to 'relative mitral sten caused by dilatation of the left ventricle or frequently, the basal diastolic murmur of ac regurgitation pericardial friction rubs and s of CHF, such as cardiomegaly persistent el tion of the sleeping pulse rate and ga rhythms Unlike some other cardiopathies rheumatic carditis cardiomegaly and heart fai do not occur unless accompanied by an org murmur

Prolongation of the PR interval can occu 40% of the patients It is useful in the diagnos rheumatic fever but not in that of clinic significant carditis (because it does not corre with organic murmurs) or in prognosis (becau does not correlate with residual heart disease

Chorea is the most curious manifestatio rheumatic fever It occurs over the most lim age range it does not occur under 3 years of and becomes rare again after puberty In adul has been rarely seen and then only in pregr women (chorea gravidarum) it has a fe predilection which increases after puberty

Chorea is also the manifestation with the st est decline in incidence (e g from 52% in 19 0% in 1975)[67] in the Western world

Involuntary and purposeless movements g

acing muscular weakness and emotional lability are the symptoms of chorea (popularly "St Vitus dance) They can occur unaccompanied by the other major manifestations with normal acute phase reactants and low ASO after a latent period longer than that of the other clinical manifestations of RF[6] The latent period between streptococcal infection and chorea may be as long as several months which makes the connection between the two events difficult indeed to explain

Patients who develop chorea as an apparently isolated manifestation have a relatively high incidence of RHD in later years (23% after 20 years) Such patients may have had before chorea but after the strep infection that caused it a mild transient carditis which caused no symptoms but sowed the seed of chronic valve disease

Subcutaneous nodules have a reported incidence between 30 and 2% they are very rare under age 3 and again in adults interestingly *they are much more frequent in the presence than in the absence of carditis* They seem to be very rare nowadays

The nodules of rheumatic fever are smaller and shorter lived *(less than 1 month) than those of* rheumatoid arthritis the olecranon is the area most frequently involved

Erythema marginatum (Fig 7) is a non pruritic pink evanescent skin rash which occurs mainly on the trunk the buttocks or the proximal parts of the limbs in the early phase of the attack but may reappear later even during convalescence[11] As the name suggests individual skin lesions expand centrifugally while the skin in the center returns to normal It appears only in patients with carditis with an incidence between 10 and 2%[3] (Fig. 7)

Among other rare manifestations *abdominal pain* can be the earliest It has been attributed to mesenteric adenitis because Yersiniosis is known to cause abdominal pain as well as arthritis and carditis[7, 73] one wonders whether these RF attacks heralded by a bellyache might not have been Yersiniosis instead

The Jones Criteria and the differential diagnosis of rheumatic fever

As every medical student knows T D Jones divided the manifestations of rheumatic fever into major and *minor according to their* diagnostic usefulness (Table VI) and proposed

Table VII Common errors in the diagnosis of rheumatic fever

1 Failure to use the Jones criteria or incorrect application of them
   a Arthralgia mistaken for arthritis
   b Day time tachycardia or prolongation of the P R interval mistaken for definite evidence of carditis
   c A physiologic systolic murmur made louder by fever—and mistaken for a pathologic murmur

Consequence A minor illness is misdiagnosed as rheumatic fever and unnecessary therapy and prophylaxis are instituted *The patient affected by cardiac non-disease* may become a "cardiac neurotic

2. Uncritical reliance on the Jones criteria
   a *Many patients may fulfill the Jones criteria yet* have other diseases (rheumatoid arthritis bacterial endocarditis congenital heart disease with congestive failure precipitated by an infection osteomyelitis lupus erythematosus etc) *Evidence of a preceding streptococcal infection will reduce* but not *eliminate the possibility of these errors*

Consequence A major disease is wrongly diagnosed as another major disease The patient may suffer not only because of the reasons listed under 1 but because treatment of the *correct disease is not given*

Table VIII Auscultatory errors

A False positive diagnosis of rheumatic heart disease

Physiologic sounds	*Erroneous interpretation*
Systolic murmur in pulmonary artery best heard along left sternal border	
a When audible at apex	Mitral regurgitation
b. When audible in aortic area	Aortic stenosis
Split 1st sound at apex with roughened 1st component and loud 2nd component	Mitral stenosis
Roughened and long 3rd sound at apex without an associated apical systolic murmur	Mitral stenosis or Acute mitral valvulitis
Gallop rhythm mimicking diastolic rumble	Mitral stenosis
Short echo effect after loud 2nd sound at base	Aortic regurgitation

B False negative diagnosis of no rheumatic heart disease

Pathologic sounds	*Error*
Short diastolic blowing murmur of aortic regurgitation along left sternal border	a. Not detected b Detected and timed as systolic
Presystolic rumble of mitral stenosis	Often not detected if patient is not exercised and put in left lateral position

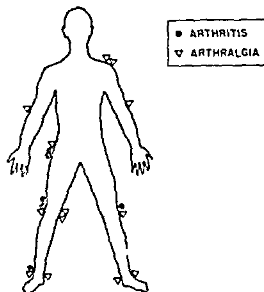


Fig 8 Joint involvement in infective endocarditis in children. Note the similarity to rheumatic fever in the predilection for large joints especially of the lower limbs From Taranta A Recent advances in diagnosis and in the prevention of rheumatic fever Bol Assoc Med P R 69 45 1977 Reproduced by permission

that the presence of two major or of one major and two minor manifestations indicates a high probability of the presence of rheumatic fever The criteria have been widely accepted and have proved useful especially in avoiding overdiagnosis In 1965 they were revised to include a confirmatory role for the preceding streptococcal infection

What most medical students (and many physicians) do not know is that the Jones Criteria are a guide not a rule they are not meant to be an exercise in diagnosis by rote or a gimmick to bypass the physician s mind

A recent review showed that 40% of the rheumatic fever cases reported to the Minnesota Rheumatic Fever Registry did not fulfill the Jones Criteria and may have been overdiagnosed[77] Fever and arthralgia was the most common presentation of these patients In fact now that subcutaneous nodules erythema marginatum and chorea are rare over diagnosis (see Tables VII and VIII) arises predominantly from misinterpretations of the signs and symptoms of arthritis and carditis arthralgia is mistaken for arthritis emotional tachycardia (absent during sleep) and prolongation of the PR interval are considered evidence of carditis and functio[nal] apical systolic murmurs are misinterpreted organic

Other and more serious errors may arise fr[om] uncritical reliance on the Jones Criteria M[any] patients may fulfill them and yet have anot[her] disease like juvenile rheumatoid arthritis c[on]genital heart diseases systemic lupus erythe[ma]tosus or osteomyelitis One should remem[ber] that streptococcal infections are common esp[eci]ally in children and therefore they can often [pre]cede an unrelated disease purely by chance G[on]ococcal arthritis is a frequent cause of acute p[oly]arthritis in the adolescent polyarthritis also [oc]curs in preicteric and anicteric viral hepatitis [and] after rubella vaccination Recently, Lyme a[rth]ritis has been described in a cluster of Conn[ecti]cut children often associated with an erythe[ma]tous skin rash it may resemble juvenile rheu[ma]toid arthritis as well as rheumatic fever[11]

In Scandinavian countries *Yersinia Entero[coli]tica* is currently a more frequent cause of arth[ritis] and carditis than RF and it has been sugge[sted] that at least in those regions *Yersinia* infec[tion] must be excluded to make a definitive diagnos[is of] RF[75] Carditis has been reported in 27% of cas[es of] Yersinia arthritis[9] However the descriptio[n of] the murmurs in most of these cases does [not] necessarily indicate organic heart lesions Fe[ver,] diarrhea often present in Yersinia arthritis [may] help in the differentiation[75, 7]

Viral carditis may mimick rheumatic f[ever] since in addition to pericarditis cardiomegaly [and] heart failure organic sounding murmurs [may] appear Of 22 cases of viral carditis eight ha[d an] apical systolic murmur three of which [were] pansystolic and five of which were loud d[e]scendo systolic murmurs with maximum int[ensi]ty at the apex[107] *As in the case of Yer[sinia]* arthritis streptococcal antibody titers may [help] in dubious cases, especially if they are con[sistent]ly negative if they are positive they may [be] coincidentally Hence viral isolation atte[mpts] and viral antibody titers may be worthwhile

The differential diagnosis of rheumatic fe[ver] includes also *infective endocarditis* espec[ially] when it presents with arthralgia or arthritis [as it] often does in children The distribution [of] affected joints is similar to that of RF (Fig [8]) *Atrial myxoma* also can present with f[ever] cardiac murmurs arthralgia elevated ESR [and] leukocytosis[8] Among blacks another sour[ce]

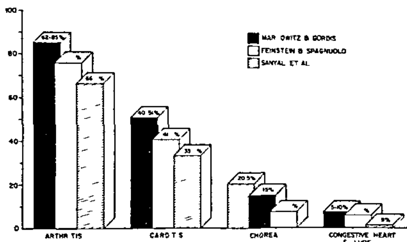


Fig 9 Similarity of the clinical profiles of the first attack of rheumatic fever in the U.S (Markowitz and Gordis and Feinstein and Spagnuolo) and Indian groups From Sanyal S K Thapar M K Ahmed S H., Hooja V., and Tewari, P The initial attack of acute rheumatic fever during childhood in North India A prospective study of the clinical profile Circulation 49 7 1974 Reproduced by permission

diagnostic confusion involving heart and joints is *sickle cell anemia* which may mimic RF because of heart murmurs and arthralgia but may also of course coexist with it [53]

As a disease decreases in incidence everything else remaining constant the proportion of false positive diagnoses will increase This has been reported for tuberculosis[3] and may well be happening now for rheumatic fever in the Western world To avoid this one needs an ever more critical stance but no more critical perhaps than suggested by T D Jones himself 34 years ago One must constantly search for laboratory and clinical evidence of other diseases [5]

Are the Jones Criteria inadequate? Diagnostic criteria are perforce arbitrary as they set up a sharp boundary between disease and non disease while no such thing exists in nature In the case of rheumatic fever it has been said that the Jones Criteria are not sufficiently sensitive especially perhaps in the developing countries and therefore children who should have this diagnosis do not and may suffer recurrences as a result On the other hand increasing sensitivity inevitably increases the percentage of false positive diagnosis which also causes suffering

Some of these problems arise from inappropriate literalness others from incompleteness of observations and data and still others from the dichotomous pattern of medical decision trees We have no problem with admitting that the boundary between health and disease is fuzzy and submit that pretending that it is sharp is of no help If a patient comes to medical attention after receiving therapy or after joint pains subsided spontaneously there is no way to tell arthritis apart from arthralgia If streptococcal antibodies are not available how can one confirm the preceding infection? But in such cases inability to confirm is fundamentally different from exclusion The prudent physician will therefore set up a category of questionable diagnoses and use it in a probabilistic manner in decision on therapy and prevention integrating it with the risks and benefits one can foresee from each

As for the reported geographic differences in the clinical pattern of rheumatic fever and therefore the need for localized Jones Criteria selection biases have never been excluded In countries where physicians are scarce and hospital beds are at a premium patients with the transient arthritis of rheumatic fever and without heart failure are unlikely to find their way into hospital services But recent careful prospective studies from India (see Fig 9)[59] and Trinidad[60] indicate that in these localities at least rheumatic fever does not differ from the garden variety and by implication that the Jones Criteria are valid there also

The role of the laboratory in the diagnosis of rheumatic fever is mainly confirmatory when it reveals the existence of a recent streptococcal infection and of a systemic inflammatory state The lack of either throws doubt on the diagnosis (with the exception of isolated chorea and of longstanding carditis) According to the revised

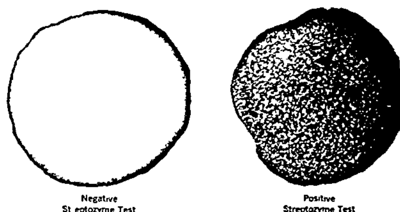


Fig 10 Streptozyme test negative and positive streptococcal passive hemagglutination test A two minute test, highly sensitive for streptococcal infections. From Janeff J Janeff D Taranta A and Cohen H A screening test for streptococcal antibodies Lab Med 2 38 1971 Reproduced by permission

Table IX Natural history of rheumatic fever

Authors and years of study	No of pts	10 years			20 years		
		Dead of RHD/SBE	No HD	RHD	Dead of RHD/SBE	No HD	RHD
Bland and Jones 1921 31	1 000	202 (20%)	323 (32%)	475 (47%)	301 (30%)	319 (32%)	380 (38%)
Ash 1922 32	537	143 (26%)	203 (38%)	191 (36%)	?	?	?
Cooperative Study 1951 52	497	19 (4%)	292 (59%)	183 (38%)	?	?	?
Irvington House (Estimated) 1952 58	599	18 (13%)	400 (67%)	181 (30%)	?	?	?

SBE = subacute bacterial endocarditis

Jones Criteria ASO titers of at least 250 units in adults and 333 in children over five years of age are considered indicative of a recent streptococcal infection *

However the ASO titer is elevated only in 70 to 80% of patients with RF therefore a low ASO titer by itself does not rule out the diagnosis In recent years the streptozyme test has been used successfully as a second streptococcal antibody test or even as a single test in lieu of the ASO or as a screen before doing the ASO It is a simple and rapid test which can even be done at the bedside (see Fig 10) and has much to recommend it although concern lingers over the reproducibility of the reagents from batch to batch

Another approach to the laboratory diagnosis of rheumatic fever is the determination of heart antibodies[45] These have been useful in selected cases but have not yet entered general use

Recurrences of rheumatic fever and evolution of rheumatic heart disease

Recurrences are a striking feature of RF which set it apart from most other diseases of infectious etiology influence markedly the prognosis of RHD and are the target against which prophylactic intervention can be most efficiently directed The frequency of recurrences in the o[ld] days and their relative rarity since secondary prophylaxis was introduced in the 1940 s is probably the main reason for the change in prognosis of RF in recent years (Table IX)

The same clinical manifestations present in the initial attack of RF tend to reappear preferentially in recurrent attacks (Table X) RF recurrences occur only among those patients who develop streptococcal antibody response and the recurrence rate per infection increases with the magnitude of the antibody rise[41] At each level o[f]

Table X Major clinical manifestation of rheumatic fever recurrences according to manifestations of the first attack*

Manifestations of first attack (isolated or combined with others)	Manifestations of recurrences (isolated or combined with others)		
	Poly arthritis	Carditis	Chorea
Polyarthritis (N = 149)	110 (74%)	51 (34%)	18 (12%)
Carditis (N = 89)	44 (49%)	62 (70%)	2 (2%)
Chorea (N = 68)	11 (16%)	10 (15%)	54 (79%)

D ta of Roth, I R Lingg C and Wittemore A Heart disease in children A rheumati group I Certain aspects of th ag at nset and f recurrences in 488 cases of juvenil rheumatism ushered in by major clinical manifest tions AM HEART J 13 36 1937

Table XI Ratio of rheumatic recurrences to streptococcal infections in patients stratified for pre existing rheumatic heart disease and for ASO rise*

ASO rise in number of tube dilutions	Pre existing heart disease	No pre existing heart disease
0-1	3 24 (13%)	1 /9 (1%)
2	10 38 (26%)	3 50 (6%)
3	6 16 (38%)	5 34 (15%)
4+	9 16 (56%)	9 26 (35%)

Fr m data f Taranta, A Kleinberg E Feinstein A R Wood H F Tursky E and Simpson R Rheum tic fever in children and adolescents IV Relation of the rheumatic fever recurrence rate pe streptococcal infecti n to the titers of treptococcal antibodies Ann Intern. Med 60(Suppl. 5) 47 1964

antibody response streptococcal infections are more likely to lead to recurrences of RF in patients with preexisting rheumatic heart disease than in those without it (Table XI)

It has long been known that the prevalence of RHD increases with the number of previous attacks (Table XII) but this is due to the increased tendency to recurrences in patients with RHD (see again Table XI) rather than to the *de novo* appearance of RHD in patients initially free of it

In the absence of recurrences new valvular lesions do not appear even in patients who had carditis in the initial attack but old valvular lesions may evolve The severity of RHD at follow up is generally proportional to the severity of the acute carditis Mitral regurgitation frequently disappears (see Fig 11) but may also

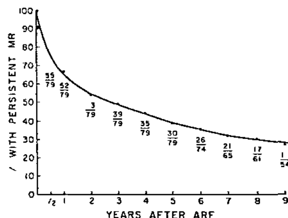


Fig 11 Persistence and disappearance of mitral regurgitation in patients maintained on continued and effective prophylaxis Follow up of 79 patients who had mitral regurgitation with their first attack In the 54 patients still followed at 9 years mitral regurgitation was still present only in 14 out of 54 (26%) From Tompkins, D G Boxerbaum B., and Liebman T Long term prognosis of rheumatic fever patients receiving regular intramuscular benzathine penicillin Circulation 45 543 1972 Reproduced by permission

Table XII Prevalence of rheumatic heart disease according to number of previous attacks of rheumatic fever*

Previous attacks	Number of patients	Number of patients with heart disease
0	797	264 (33%)
1	280	170 (60%)
2	57	43 (75%)
3	31	25 (81%)
4	4	4 (100%)

Adapted from Taranta, A., Kl inberg E F instein, A R., Wood H. F Tursky E nd Simpson R. Rh umatic fever in children and adolescents IV Relation of th rheumatic fev recurrence rate per streptococcal infect on to th titers of streptococcal antibodies, Ann Intern Med 60(S pp 5) 47 1964

worsen mitral stenosis may gradually develop aortic regurgitation once it becomes symptomatic runs usually a rapid downhill course [4] and aortic stenosis in combination with regurgitation may slowly appear (by contrast pure aortic stenosis is almost never rheumatic [90])

What causes the progression of valvular disease in the absence of clinically detectable recurrences is uncertain The absence of mitral stenosis on follow up of some populations of children maintained on rigid (benzathine penicillin) antirheumatic prophylaxis[93] makes one wonder whether

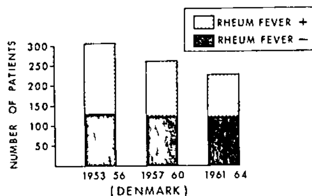


Fig 12 Incidence of rheumatic heart disease in Denmark with and without a history of acute rheumatic fever Notice that a decrease occurred only in the group with such history From Vendsborg P Faverholdt L and Olesen K H Decreasing incidence of a history of acute rheumatic fever in chronic rheumatic heart disease Cardiologia 53 332 1968 Reproduced by permission

Table XIII Causes of mitral regurgitation in necropsy patients older than 14 years*

Cause	*Number of patients*	
Rheumatic	30	
Rupture of chordae tendineae in previously normal valve	15	
Floppy valve	4	
Congenital	4	
Corrected transposition		1
Partial A V canal		1
Endocardial fibroelastosis		1
Parachute valve		1
Possible annular calcification	1	
Uncertain	1	
Total (20 males 35 females)	55	

From Roberts W and Perloff J K A clinico pathologic survey of the conditions causing the mitral valve to function abnormally Ann Intern Med 77 939 1972

clinical or subclinical recurrences might be necessary for the development of mitral stenosis Alternatively or adjunctively the altered blood flow pattern caused by the initial lesion may alter the valve further in a slow vicious circle

Valvular heart disease and its differential diagnosis

More than 50% of patients with valvular heart disease of the kind traditionally considered rheumatic deny any history of RF attacks It was formerly assumed that all of these patients had had an attack of isolated silent rheumatic carditis that is carditis without symptoms of heart failure or of pericarditis and therefore undiagnosed While this scenario is clearly possible and must account for a fraction of such patients other etiologies occur also and are being recognized with increasing frequency

In the young the differential diagnosis with *congenital malformations* is mandatory in western countries the ratio of congenital heart disease to RHD in college students is 4 1[95] and the majority of children undergoing mitral valve replacement have congenital heart disease[96] (in India by contrasts 77% of such patients had RHD)[97] In a review of 55 cases of mitral disease in infants (an age group of course immune from rheumatic fever) 29 had primary malformation of the valve and 26 had mitral valve dysfunction due to papillary muscle infarction consequent to other malformations[98]

In 55 necropsy patients more than 14 years of age *isolated mitral disease* causing pure regurgitation was found to be non rheumatic almost as often as rheumatic[99] (Table XIII) The relatively high incidence of non rheumatic etiologies in this autopsy series may be due to the higher mortality rate of non rheumatic mitral regurgitation particularly of ruptured chordae tendineae

Isolated aortic valve disease is almost never rheumatic in a review of 139 cases of aortic valvulopathy the incidence of congenitally malformed aortic valves was 72% with very low incidence of previous history of RF and absence of Aschoff bodies[100] More frequent causes were arteriosclerotic heart disease bicuspid aortic valve infective endocarditis and ankylosing spondylitis In a Scandinavian study a marked decrease in cases of RHD over the period 1953-64 was accounted for by a decrease of patients with history of RF, while the group with no such history remained unchanged (Fig 12)[1] This also suggests that patients with findings compatible with RHD but no history of RF may have a non rheumatic cause

Both *Yersiniosis* and *viral carditis* as mentioned earlier may cause syndromes which clinically overlap with the spectrum of rheumatic fever manifestations could they also in some cases be responsible for chronic valvular disease? A recent 1½ to 3 year follow up of seven patients with *Yersinia* carditis showed only ECG abnormalities in one[1] but larger long term follow up may be worthwhile

A viral etiology has been proposed for RHD cases without history of RF and also for RF and RHD in general[1] [103] Cardiotropic viruses like Coxackie B have been demonstrated by immuno fluorescent techniques in the myocardium of patients from routine autopsies[1 4] and in as many as 73% of atrial biopsies taken during cardiac surgery[10]

Experimental infection with cardiotropic viruses in monkeys have caused valvular heart disease[106] On the clinical side persistence of seemingly organic murmurs has been reported for at least 6 to 8 months after acute viral carditis in three cases[107] So the possibility that some cases of chronic valvular disease in man may be caused by viruses must be considered That viral infections cause the garden variety of rheumatic fever however, is unlikely since penicillin prevents rheumatic fever and is ineffective against viruses–unless one postulated for viral agents a necessary but not sufficient co factor role

The rheumatic etiology of MS has also been questioned in some cases of *Lutembacher Syndrome* deformities of the mitral valve were found without evidence of previous endocarditis or thrombosis suggesting that the mitral valve pathology is due to fibrotic reaction to altered flow patterns[108] In another series of five well studied cases however four had a history of rheumatic fever[109]

Mitral valve prolapse and RHD Mitral valve prolap e (MVP) is a syndrome characterized by "non ejection systolic clicks and mitral systolic murmurs accompanied by anginal symptoms cardiac arrhythmias and ECG abnormalities[89 1 0 113] It is of interest in connection with RHD because (1) its physical signs overlap in part with those of rheumatic mitral valve disease and may therefore be misdiagnosed or such and also (2) because RF may be one of its causes Its study is not made any easier by the wild variations of its reported prevalence which has varied tenfold even in the same laboratory according to the "index of suspicion and the related carefulness of the physical examination

The overlap between rheumatic mitral regurgitation and mitral valve prolapse is exemplified by a series of 130 cases of MVP rheumatic etiology was considered probable in eight and definite in 13 on the basis of history[1] (Fig 13) In another clinic 18 5% of 185 cases of rheumatic carditis characterized initially by blowing pansystolic murmurs developed late or mid late systolic murmurs between one month and 9 years after the attack[1 3] and of 12 patients with previous rheumatic fever and late systolic murmur ten were shown to have mitral valve prolapse by echocardiography

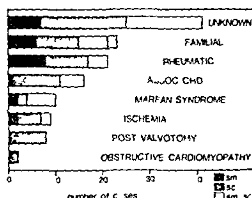


Fig 13 Probable etiology of mitral valve disease in 130 patients with late systolic murmurs *(sm)* non-ejection systolic clicks *(sc)* or both From Pocock, W A and Barlow J B Etiology and electrocardiographic features of the billowing posterior mitral leaflet syndrome Am J Med. 51 731 1971 Reproduced by permission

In Soweto South Africa the prevalence of non ejection systolic clicks seemed to parallel that of RHD This led to the hypothesis that MVP might represent early RHD[1] However a follow up study of children with MVP showed neither rheumatic attacks nor clinical deterioration on no prophylaxis Obviously the relation of RHD and MVP remains an intriguing one for investigation

We have certainly come a long way from 1924 when Coombs could state that all acquired mitral valve disease also all unexplained cardiomegaly in children are rheumatic because no alternative theory of causation is available[11] (Fig 14)

Treatment

It is ironic that the field most important to a physician treatment is the one that can boast the least progress To be sure surgery has provided relief for the most disabling end results of carditis but the outcomes are often imperfect the operative mortality rate not negligible and whenever prostheses are involved the postoperative risk of infective endocarditis is significant and the need for perennial anticoagulation is bothersome Most important perhaps from a

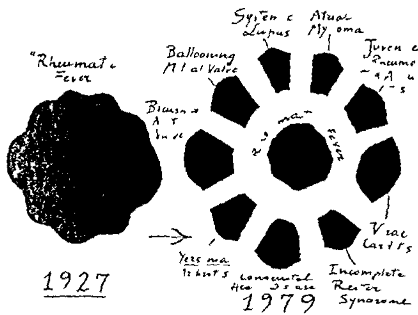


Fig 14 The whittling away of rheumatic fever Many diseases that had not been described or were difficult to diagnose in 1927 (the particular year is arbitrary) were "lumped" into rheumatic fever (in the presence of fever) or with rheumatic heart disease (in its absence) They are now split off What remains is a core smaller but more homogeneous than the original lump

Table XIV Effect of salicylate on acute rheumatic fever*

	Treatment	
	Sodium salicylate (N = 60)	*Placebo (alkali)* (N = 60)
Average duration of fever	5 7 days	10 7 days
Average duration of joint swelling	5 0 days	12.2 days
Development of carditis under observation	11 6%	6 6%
Relapses	26.6%	8 3%

* From Finlay D W and Lucas, R H. Lancet 2 420 1879

world wide standpoint cardiac surgery is often unavailable or difficult to get to or rudimentary in many parts of the world—the very parts in fact where the need is greatest

Medical therapy still revolves around aspirin steroids, and bed rest As the antique study of Finlay and Lucas (Table XIV) already showed salicylates are effective on arthritis but not on carditis and may increase the percentage of relapses which we would now call rebounds But only a few points are buttressed by controlled studies the following therefore reflects our biases as much as our knowledge

All patients with rheumatic fever should be examined daily for the first 2 or 3 weeks of the illness primarily to find out whether carditis develops and to start treatment should heart failure appear Discussion at the bedside concerning heart murmurs or cardiomegaly are best avoided often the patient misunderstands and worries needlessly

All patients should be in bed for the first 3 weeks of illness because *carditis* if not already present may appear during this period. Strict bed rest however, should be limited to patients with arthritis of the lower limbs and to those with carditis and a large heart The bed rest regime should then be tailored to the manifestations of the disease that are present in the particular patient Those with *polyarthritis* only are usually asymptomatic by the second or third weeks of aspirin treatment They may then be gradually ambulated while continuing on aspirin. *Patients with significant murmurs but no definite cardiomegaly or heart failure* (with or without polyarthritis) should be kept in bed for 2 to 3 The bed rest need not be strict, and in the last week may be broken by periods of supervised ambulation of a few hours per day *Patients with carditis and cardiomegaly but no congestive heart failure* (with or without polyarthritis) should be kept on bed rest for 6 weeks the first

weeks of which should be strict Patients with carditis and congestive heart failure (with or without polyarthritis) should be kept on strict bed rest until failure is controlled It is wise to maintain a modified bed rest until a month after anti inflammatory treatment is stopped (if no rebound ensues) or until 2 weeks after the spontaneous subsidence of a rebound

In cases with arthralgia only or with mild arthritis and no carditis the patient may be given analgesics only This is particularly wise when the diagnosis is not definite *Patients with moderate or severe arthritis but no carditis or with carditis but no cardiomegaly* or failure will be treated with aspirin two thirds to three fourths grains per pound per day for the first 2 weeks and one half grain per pound per day for the following 6 weeks Sometimes slightly larger doses may be necessary to control arthritis *Patients with carditis and cardiomegaly but no congestive heart failure* (with or without polyarthritis) should be started on aspirin (see above) In patients with marked cardiomegaly however aspirin is often insufficient to control fever discomfort and tachycardia or does so only at toxic or near toxic doses These patients may then be switched to steroids (see below)

Patients with carditis and heart failure (with or without polyarthritis) should receive prednisone, starting with a dose of 40 to 60 mg per day to be increased if control of heart failure is not achieved In cases of extreme acuteness and severity therapy should be started by intravenous administration of methylprednisone (Solu Medrol 10 to 40 mg) followed by oral prednisone After 2 or 3 weeks, prednisone may be slowly withdrawn decreasing the daily dose at the rate of 5 mg every 2 or 3 days and adding aspirin at standard doses Aspirin should be continued for 3 or 4 weeks after prednisone is stopped This overlap therapy reduces the incidence of post therapeutic clinical rebounds

The termination of anti inflammatory treatment may be followed in all rheumatic fever patients by the reappearance within 2 or 3 weeks of laboratory abnormalities (laboratory rebounds) or of clinical abnormalities as well (clinical rebounds) All the laboratory rebounds and most of the clinical rebounds are best left untreated or should be treated symptomatically with analgesics or small doses of aspirin lest the full treatment be followed by another rebound and the duration of the attack be lengthened Only the most severe clinical rebounds necessitate reinstitution of the full original treatment [3]

Unfortunately most well controlled studies have failed to prove that treatment with steroids decreases the incidence of residual rheumatic heart disease [1] [1] Nevertheless such treatment is indicated in patients with severe carditis and failure because of the distinct impression that death during the acute attack may be averted thereby [1]

In about 5 to 10% of all patients with rheumatic fever a persistently elevated erythrocyte sedimentation rate is observed for months after termination of therapy This is a benign unexplained phenomenon that should not alter the medical management [1] However a persistently elevated C reactive protein level often heralds a protracted course with subsequent flare ups these patients should be supervised closely Once rheumatic fever has subsided and more than two months have gone by after stopping treatment with aspirin or steroids rheumatic fever does not reappear unless a new streptococcal infection occurs [1,2]

The heart failure of rheumatic carditis is often controlled with bed rest and steroids only If it isn t diuretics may be added first followed by digitalis if needed Digitalis should be used with caution because its therapeutic range may be decreased in rheumatic carditis The need for digitalis should be reevaluated at the end of the rheumatic attack and periodically thereafter In assessing the effect of digitalis one should distinguish cardiac tachycardia which is also present during sleep (sleeping tachycardia) from emotional tachycardia which subsides during sleep

Patients with *chorea* may benefit from administration of barbiturates or tranquilizers Since chorea often occurs as an isolated manifestation or a few months after arthritis or carditis anti inflamatory medication is not usually needed

Prevention of rheumatic fever recurrences

For all its simplicity and lack of glamour, prevention of recurrences is the finest achievement of medicine in rheumatic fever It is markedly effective in reducing and in fact practically in eliminating recurrences when benzathine penicillin is used Moreover the success of secondary prophylaxis is way out of proportion to th

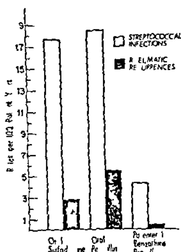


Fig 15 Streptococcal infection rates and rheumatic recurrence rates per 100 patient years in children and adolescents with previous rheumatic fever The three prophylactic regimes were tested concurrently sulfadiazine 1g/day orally in a single dose (675 patient years) penicillin G 0.2 million units/day orally in a single dose ½ hour before breakfast (545 patient years) and benzathine penicillin G 1.2 million units intramuscularly every 4 weeks (560 patient years) From Taranta A and Gordis L. The prevention of rheumatic fever Opportunities frustrations and challenges Cardiovasc Clin 4 1 1972 Reproduced by permission

purely numerical reduction of rheumatic fever attacks because a disproportionate number of deaths and disabilities are due to recurrences rather than to first attacks In fact the much touted change in clinical pattern of the disease in the Western world is largely due to the reduction of recurrences

As soon as the diagnosis of rheumatic fever is made—not sooner lest other possible diagnoses be obscured—the patient should be started on anti streptococcal prophylaxis with an initial thera peutic (streptococcal eradicating) dose or course of antibiotics (as outlined under *Appropriate treatment* below) Thanks to this eradicating treatment one can then start continual prophy laxis with a clean slate and clearly identify new infections should they occur

Best results are obtained with the injection of 1 2 million units of benzathine penicillin G every four weeks' ⁵ (Fig 15) This is the treatment of choice it is especially useful in high risk patients—i e those with rheumatic heart disease or with a recent previous attack (3 years or less) or with multiple attacks or those unlikely to take diligently a daily medication Additional risk factors are young age (childhood and adoles cence) exposure to young people and crowd the home In patients intolerant of benz penicillin because of pain at the site of inj continual oral medication may be prescrib success of course depends on the complia the patient which may be poor even wh patient seems to be cooperative [131]

Sulfadiazine (0 5 g once daily in cl weighing less than 60 pounds and 1 g others) and oral penicillin (200,000 to units twice a day) are about equally effec Patients on sulfadiazine should have a count after 2 weeks and also wheneve develop a rash in association with fever throat The drug should be stopped if th count falls below 4 000 and the neutroph falls below 35 per cent For the exce patient who may be sensitive to both pe and sulfa erythromycin may be prescrib to 250 mg twice daily [133])

For maximum protection continual pro is may be maintained for the lifetime patient This is particularly importa patients with rheumatic heart disease T factors mentioned earlier may serve as a the physician so he may apply pressu persuasion in accordance with the n protection of the particular patient [134]

Prevention of first attacks

The prevention of recurrences is usefu to patients after a first attack but will n definition eradicate the disease The h some patients are forever damaged by attack to them the triumphs of se prophylaxis are no consolation Though effective when it can be administered pro of first attacks is hampered by the huge si population at risk and by the limitation ability to diagnose streptococcal pharyng mostly because of the limitations of pre primary prevention that hopes are pinne vaccine (see below) In the meantime a l accomplished by the diligent and im application of existing knowledge

Patients with fever fiery red thro exudate and tender anterior cervica nodes [3] are more likely than others t streptococcal pharyngitis but even this picture may be caused by viruses Co some mild sore throats may be streptoc

may be followed by rheumatic fever or glomerulonephritis Therefore, it is considered prudent* to take a throat culture in all patients with acute pharyngitis and to treat all those with a positive culture[137] even though economic considerations may suggest otherwise[38, 139] Hoarseness conjunctivitis cough and simple coryza are usually *not* associated with streptococcal infections, therefore patients with these symptoms need not be cultured

The technique of taking a throat culture is simple but often neglected The throat culture should be taken of course *before* antibiotic therapy The tongue should be depressed the throat should be clearly visualized and well lit and the swab must be rubbed vigorously over each tonsillar area without touching the tongue or the lips One may then send the swab to a laboratory following the laboratory s instructions or one may streak the swab directly on a blood agar plate and then incubate and read the plate[1] Taking two cultures decreases the incidence of false negatives[141] *The cost of the throat culture* which is often excessive can be reduced by using state laboratories (whenever available) or by doing the culture in one s own office Alternatively one may ask commercial or hospital laboratories to omit the unnecessary garnishes of identification of all bacterial species (usually the only important organisms to identify are group A beta hemolytic streptococci) and of antibiotic sensitivity (all group A beta hemolytic streptococci are sensitive to penicillin)[1]

When to start treatment and whether to start treatment without a throat culture depends on how sick the patient is and on how compliant he is considered to be and of course on the availability of throat cultures Treatment may be started at once in a febrile toxic patient with exudative pharyngitis This is particularly true for those patients who may not be expected to return for treatment Often in emergency room practice or walk in clinics the doctor perceives that the patient is not likely to come back and that treatment will be given either now or never he should then treat now On the other hand the milder the symptoms and signs and the closer the patient–doctor relationship the safer it is to delay treatment until an etiologic diagnosis is made One should remember that a few days delay in initiating treatment has been shown not to be harmful in terms of rheumatic fever prevention[1, 3]

Although many parents of patients are anxious to obtain instant treatment experience has shown that they can be educated In fact in increasing numbers of middle class communities mothers rate pediatricians on the basis of their throat culturing habits[1]

If treatment is started with an oral agent before the culture results are known the options remain open to discontinue medication the morning after if the throat culture is negative for beta hemolytic streptococci or to discontinue medication one day later if they are not of group A

Appropriate treatment Given the present state of knowledge eradication of streptococci from the throat is the aim of treatment not only to prevent rheumatic fever but to interrupt the chain of contagion Eradication depends upon the choice of drug and the length of time effective blood levels are maintained

Penicillin is the drug on which the largest amount of favorable data have been accumulated It can be administered by the oral route (200 000 to 250 000 units three to four times a day or even twice daily[33] at least ½ hour before or 1 hour after meals for 10 days even though symptoms will abate earlier Advantages of the oral route are a lower incidence of severe allergic reactions and the option to discontinue the drug if the diagnosis is not confirmed by culture or if allergy develops

Buffered penicillin G the least expensive preparation seems to be just as effective in the treatment of streptococcal pharyngitis as penicillin V or phenethicillin The chief drawback is failure to complete the prescribed course Such failure is surprisingly common especially in clinic or emergency room patients[1, 4] presumably because the patient his parents and at times the doctor do not understand why one should treat a sore throat that is no longer sore Of course the main reason for treatment is prevention of rheumatic fever and protection of contacts—not the amelioration of symptoms which is not marked at best[45]

The most reliable way to guarantee adequate therapy is by a single injection of benzathine penicillin G[145] 0 6 million units in children weigh

*Prudence is for the ben fit of th physician n less than the patient f want of a throat culture a lawsu t may be lost[44]

ing less than 60 pounds or 1.2 million units in the others[17] If a combination of procaine penicillin and benzathine penicillin is used the latter should still be given in the amounts just noted

Penicillin allergy is a cause of genuine concern especially when dealing with adults Care should be taken to obtain a good history and to keep epinephrine (adrenalin) at hand

For patients with a history of penicillin allergy *rythromycin* should be prescribed 20 mg per pound per day in divided doses (not to exceed 1 g per day) for 10 days

Sulfonamides which are effective in secondary prevention should not be used in primary prevention because they do not eradicate group A streptococci *Tetracyclines* should not be used for he same reason[14]

In some parts of the world where broad spectrum antibiotics have been used with largesse resistance to many antibiotics including erythromycin lincomycin and chloramphenicol is spreading among streptococci Sensitivity to penicillin persists so far[19]

Family members of a patient with symptomatic streptococcal pharyngitis are at a high risk of being infected It seems prudent therefore to culture all family contacts with recent upper respiratory symptoms and to treat those with positive cultures Some physicians elect to treat all family contacts

There are several good reasons to schedule *follow up visits* to ascertain whether the infection has cleared or is relapsing to stimulate compliance in patients on oral medication and to find out whether streptococcal sequelae have resulted In the case of oral medication the follow up visit should be set at 2 to 10 days after the estimated end of a bactericidal concentration (14 to 16 days for 600 000 units and 21 to 28 days for 1 2 million units of benzathine penicillin)

Streptococcal relapses can be clinical and bacteriologic (sore throat with positive throat culture) or bacteriologic only (positive throat culture without sore throat)

Current recommended practice is to treat both kinds of recurrences with a second course of penicillin (preferably benzathine penicillin by injection) or erythromycin by mouth

Rheumatic heart disease predisposes to *infective endocarditis* It is advisable to administer appropriate antibiotics to patients with rheumatic heart disease whenever they are exposed t procedure which causes bacteremia

Anti streptococcal vaccine

For all the successes of antibiotics and che therapeutic agents infectious diseases have l eradicated only by vaccines (or environme sanitation) Hence the long history of attemp develop a streptococcal vaccine and the int study of M proteins the only streptococcal c ponents that elicit protective antibodies T efforts have long been frustrated by the failu obtain preparations at once highly antigenic well tolerated Until recently even highly p fied M protein preparations elicited del hypersensitivity reactions which seemed to directed not to the type specific determinant, to a common non type specific antigen associated protein or MAP)[22]

The classic method of preparing M pro entails hot acid extraction of the bacterial cel its first step By extracting the cells with peps physiologic temperature instead of the more d tic procedure Beachey and associates[23] l obtained a preparation of M protein that is hi immunogenic and yet free of non type spe immunoreactivity and cross reactivity with h antigens This important achievement paves way for the preparation of multivolent non t streptococcal vaccines for human use

REFERENCES

1 Vendsborg P., Faverholdt L. and Olesen, K. Decreasing incidence of a history of acute rheu fever in chronic rheumatic heart disease Cardio 53 332 1968

2 Markowitz M The changing picture of rheu fever Arthritis Rheum 20 369 1977

3 Quinn R. W and Federspiel C The inciden rheumatic fever in metropolitan Nashville A Epidemiol 99 273 1974

4 Gordis L. Lilenfeld A and Rodriguez R. Studi the epidemiology and preventability of rheumatic f I Demographic factors and the incidence of a attacks J Chronic Dis 21 665 1969

5 Mortimer E A Control of rheumatic fever Ho we doing? (Editorial) J.A M.A. 237 1720 19

6 Gordis L. Effectiveness of comprehensive programs in preventing rheumatic fever N Eng Med. 289 331 1973

7 Glassman Carl New York Times January 23, 19

8 Quinn R W., and Federspiel, L F The occurren hemolytic streptococcus in school children in Nash Tennessee 1961-68 Am J Epidemiol. 97 2 1973

9 Shiokawa Y., and Yamada T Epidemiology of r matic fever and rheumatic heart disease with su

lance of hemolytic streptococcus Japn Circ J 41 167 1977
10 McLaren M J Hawkins, D M Koornhof H J Bloom K R., Bramwell-Jones O M Cohen E., Gale G E, Kanarek K., Lachman A S., Lakier J B Pocock, W A and Barlow J B Epidemiology of rheumatic heart disease in black school children of Soweto Johannesburg Br Med J 3 474 1975
11 Harold Houser Personal communication
12 Ayuthya P S N Ratanabanangkoon K and Pongpanich, B Juvenile rheumatic fever and rheumatic heart disease at Rhamathibodi Hospital Thailand Southeast Asian J Trop Med Public Health 7 77 1976
13 D'Arbela P G Patel, A K., and Somers K Juvenile rheumatic fever and rheumatic heart disease at Mulago Hospital Kampala Uganda some aspects of the pattern of the disease E Afr Med J 51 710 1976
14 Stanfield, J P., and Bracken P M ASO titers in the childhood population in rural and semi rural Uganda E. Afr Med. J 50 153 1973
15 Seltzer A and Cohn, K E Natural history of mitral stenosis A review Circulation 45 878 1972
16 Bailey C P., and Bolton H E Criteria for and results of surgery for mitral stenosis, N Y State J Med 56 825 1956
17 Cherian G Vytlingam K I Sukumar I P and Gopinath N Mitral valvotomy in young patients, Br Heart J 26 157 1964
18 Stollerman G H Siegel A C and Johnson E E Variable epidemiology of streptococcal disease and the changing pattern of rheumatic fever Mod. Concepts Cardiovasc. Dis 34 45 1965
19 Swanson J., Hsu K and Gotschlich E Electron microscopic studies of streptococci. I M antigen J Exp Med. 130 1063 1969
20 Ofek I Beachey E H., Jefferson W and Campbell, G L Cell membrane binding properties of group A streptococcal lipoteichoic acid J Exp Med. 141 990 1975
21 Wittner M K and Fox E N Homologous and heterologous protection of mice with group A streptococcal M protein vaccines Infect Immun 15 104 1977
22 Beachey E H and Stollerman G H The common antigen(s) of streptococcal M protein vaccines causing hyperimmune reactions in man Trans Assoc Am Physicians 85 212 1972
23 Cunningham M and Beachey E H Immunochemical properties of streptococcal M protein purified by isoelectric focusing J Immunol. 115 1002 1975
24 Widdowson, J P., Maxted W R and Pinney A M Immunological heterogeneity among the M associated protein antigens of group A streptococci, J Med Microbiol. 9 73 1976
25 Widdowson J P Maxted W R and Pinney A M An M associated protein antigen (MAP) of group A streptococci J Hyg Camb 69 553 1971
26 Widdowson J P Maxted W R Grant D L and Pinney A M The relationship between M antigen and opacity factor in group A streptococci, J Gen. Microbiol. 65 69 1971
27 Zabriskie J B Mimetic relationships between group A streptococci and mammalian tissues Adv Immunol 7 147 1967
28 Kaplan M H and Meyeserian M An immunological cross-reaction between group A streptococcal cells and human heart tissue Lancet 1 706 1962
29 Markowitz A S and Lange C F Jr Streptococcal related glomerulonephritis I Isolation immunochemistry and comparative chemistry of soluble fractions from Type 12 nephritogenic streptococci and human glomeruli, J Immunol. 92 565 1964
30 Rapaport R T Chase, R M Jr and Solowey A C Transplantation antigen activity of bacterial cells in different animal species and intra-cellular localization Ann N Y Acad Sci. 129 102 1966
31 Zabriskie J B and Freimer E H An immunological relationship between the group A streptococcus and mammalian muscle J Exp Med. 124 661 1966
32 Lyampert I M., Danilova T A., Borodyuk, N Y and Beletskaya L V Mechanism of formation of antibodies to heart tissue in immunization with group A streptococci, Folia Biol Praha 12 108 1966
33 Lyampert I M Vvedenskaya O I., and Danilova T A Study on streptococcus Group A antigens common with heart tissue elements, Immunology 11 313 1966
34 Goldstein I Halpern B., and Robert L Immunological relationship between streptococcus A polysaccharide and the structural glycoproteins of heart valve Nature 213 44 1967
35 Holm S E Precipitinogens in beta hemolytic streptococci and some related human kidney antigens, Acta Pathol. Microbiol Scand 70 79 1967
36 Sandson J Hamerman, D., Janis R and Rojkind M Immunologic and chemical similarities between the streptococcus and human connective tissue Trans Assoc Am Physicians 81 249 1968
37 Hirata A A., and Terasaki, P I Cross reactions between streptococcal M proteins and human transplantation antigens Science 168 1095 1970
38 Husby G., van de Rijn I., Zabriskie J B Abdin Z H and Williams, R C Jr Antibodies reacting with cytoplasm of subthalamic and caudate nuclei neurons in chorea and acute rheumatic fever J Exp Med 144 1094 1976
39 Dudding B A and Ayoub E M Persistence of streptococcal group A antibody in patients with rheumatic valvular disease J Exp Med. 128 1081 1968.
40 Zimmerman R A., Auernheimer A H., and Taranta A Precipitating antibody to group A streptococcal polysaccharide in humans, J Immunol. 107 832 1971
41 Ayoub E M., Taranta A., and Bartley T D Effect of valvular surgery on antibody to the group A streptococcal carbohydrate Circulation 50 144 1974
42 van de Rijn I Zabriskie J B and McCarty M Group A streptococcal antigens cross reactive with myocardium Purification of heart reactive antibody and isolation and characterization of the streptococcal antigen J Exp Med 146 579 1977
43 McLaughlin J F., Paterson P Y., Hartz, R S and Embury S H Rheumatic carditis in vitro responses of peripheral blood leukocytes to heart and streptococcal antigens Arthritis Rheum 15 600 1972
44 Yang L C Soprey P R Wittner M K., and Fox E N Streptococcal induced cell mediated immune destruction of cardiac myofibers in vitro J Exp Med. 146 344 1977
45 Wannamaker L W and Ferrieri, P Streptococcal Infections Updated. Disease a Month, Chicago 1975 Year Book Medical Publishers, Inc.
46 Kaplan E L., and Wannamaker L W Streptolysin O Suppression of its antigenicity by lipids extracted from skin Proc Soc Exp Biol. Med 146 205 1974
47 Bisno A. L., Pearce I A., Wall, H. P Moody M D., and Stollerman G H Contrasting epidemiology of acute rheumatic fever and acute glomerulonephritis

Nature of the antecedent streptococcal infection N Engl J Med 283 561 1970
48 Potter E V Svartman M., Mohammed, I Cox R Poon King T., and Earle D P Tropical acute rheumatic fever and associated streptococcal infections compared with concurrent endemic and early epidemic acute glomerulonephritis J Pediatr 92 325 1978
49 Rammelkamp C H., Jr Harvey Lectures Series 51 113 1955 56
50 Kuttner A G and Krumwiede E Observations on the effect of streptococcal upper respiratory infections on rheumatic children A three year study J Clin Invest 20 273 1941
51 Widdowson J P Maxted W R., Notley C M., and Pinney A M The antibody responses in man to infection with different serotypes of group-A streptococci, J Med Microbiol. 7 483 1974
52 Stollerman G H Nephritogenic and rheumatogenic group A streptococci, J Infect Dis 120 258 1969
53 Taranta A Torosdag S Metrakos J., Jegier W., and Uchida I Rheumatic fever in monozygotic and dizygotic twins. Proceedings of the Tenth International Congress of Rheumatology Minerva Medica Torino 1961 pp 96-98
54 Spagnuolo M and Taranta A. Similarity in the clinical manifestations of rheumatic fever in siblings N Engl. J Med 278 183 1968
55 Zabriskie J B Presented at the American College of Physicians meeting on hypersensitivity and collagen diseases February 1977
56 Caughey E D Douglas R Wilson W and Hassall, I B HLA antigens in Europeans and Maoris with rheumatic fever and rheumatic heart disease J Rheumatol. 2 319 1975
57 Greenberg L J Gray E D and Yunis E J Association of HLA 5 and immune responsiveness in vitro to streptococcal antigens, J Exp Med 141 935 1975
58 Lueker R D and Williams R C Jr Decreased reactivity of lymphocytes in mixed leukocyte culture from patients with rheumatic fever Circulation 46 655 1972
59 Sanyal, S K Thapar M K Ahmed S H., Hooja V and Tewari, P The initial attack of acute rheumatic fever during childhood in North India A prospective study of the clinical profile Circulation 49 7 1974
60 Potter E V Svartman M Mohammedi, I Cox R Poon King, T and Earle D P Tropical acute rheumatic fever and associated streptococcal infections compared with concurrent acute glomerulonephritis J Pediatr 92 325 1978
61 McDanald E C and Weisman M H Articular manifestation of rheumatic fever in adults Ann Intern Med. 89 917 1978
62 Leinslao M., and Laitinen O Rheumatic fever in adult patients Ann Clin Res 7 244 1975
63 Ruderman J E and Abruzzo J L Chronic post rheumatic fever arthritis (Jaccoud s) report of a case with subcutaneous nodules Arthritis Rheum 9 640 1966
64 Kaludi M and Duranceau L Le Syndrome de Jaccoud Union Med Can 105 1609 1976
65 Clarke M and Keith J D Atrioventricular conduction in acute rheumatic fever Br Heart J 34 472 1972
66 Osler W On chorea and choreiform affections Philadelphia 1894 P Blakiston Son & Co
67 Leinslao M Abstract XIV International Congress of Rheumatology San Francisco CA June 26-July 1 1977 p 129
68 Taranta A. and Stollerman G H The relatio Sydenham s chorea to infection with group A r cocci, Am J Med 20 170 1956
69 Bland E F Chorea as a manifestation of rheu fever a long term perspective Trans Am Clin C tol. Assoc 73 209 1961
70 Massel B F Mote J R and Jones, T D artificial induction of subcutaneous nodules in pa with rheumatic fever J Clin Invest 16 25 193
71 Burke J B Erythema Marginatum, Arch. Dis (30 359 1955
72 Feinstein A R and Spagnuolo M The c patterns of acute rheumatic fever a reappraisal, cine 41 279 1962
73 Massel, B F., Fyer D C and Roy S B The c picture of rheumatic fever diagnosis, immedia nosis course and therapeutic implications, Am. J diol. 1 436 1958
74 Jacobs, J Yersinia enterocolitica arthritis, Ped. 55 236 1975
75 Laitinen O Leinslao M and Allander E Rheu fever and Yersinia arthritis Criteria and diag problems in a changing disease pattern Scand. J matol. 4 145 1975
76 Stollerman G H., Markowitz M Taranta A W maker L. W and Wittemore R Jones Cr (revised) for guidance in th diagnosis of rheu fever Circulation 32 664 1965
77 Dahl, D Bessinger F B and Kaplan, E L. Rheu ic fever in Minnesota Current assessment of rep cases Minn Med 61 249 1978
78 Steere A C Malawista S E Snydman, D R., S R E Andiman W A Ross M R and Steele, Lyme arthritis An epidemic of oligoarticular arthr children and adults in three Connecticut commu Arthritis Rheum 20 7 1977
79 Leino R and Kalliomaki, J L. Yersiniosis internal disease Ann Intern Med. 81 458 19 4
80 Taranta A Recent advances in diagnosis and prevention of rheumatic fever Bol. Assoc Med 69 45 1977
81 Janeff J., Janeff D Taranta A and Cohen, screening test for streptococcal antibodies, Lab. 2 38 1971
82 Lortscher R H., Toews W H Nora J J Wolfe and Spangler R A. Atrial myxoma presenti rheumatic fever Chest 66 307 19 4
83 Mazzara J T Burns G C Mueller H S and S M Coexistence of sickle cell anemia and rheu heart disease N Y State J Med 71 24 6 19 1
84 Boyd, J C and Marr J J Decreasing reliabi acid fast smear techniques for detection of tuber Ann. Intern Med 82 489 1975
85 Jones T D The diagnosis of rheumatic fever JA 126 481 1944
86 Zabriskie J B Hus K C and Seegal, B C. reactive antibody associated with rheumatic Characterization and diagnostic significance Clin. Immunol. 7 147 1970
87 Bland E F., and Jones T D Rheumatic fever rheumatic heart disease—a 20 year report on patients followed since childhood Circulation 1951
88 Ash R The first 10 years of rheumatic infectio childhood Am Heart J 36 89 1948
89 U K and U S Joint Report The natural his rheumatic fever and rheumatic heart disease co tive clinical trial of ACTH cortisone and aspirin C lation 32 457 1965

90 Roth, I R Lingg C., and Wittemore A Heart disease in children A rheumatic group I Certain aspects of the age at onset and of recurrences in 488 cases of juvenile rheumatism ushered in by major clinical manifestations Am Heart J 13 36 1937
91 Taranta A Kleinberg E Feinstein A R Wood H F Tursky E. and Simpson R Rheumatic fever in children and adolescents IV Relation of the rheumatic fever recurrence rate per streptococcal infection to the titers of streptococcal antibodies Ann Intern Med. 60 (Suppl. 5) 47 1964
92 *Ibid*
93 Tompkins, D G Boxerbaum B and Liebman T Long term prognosis of rheumatic fever patients receiving regular intramuscular benzathine penicillin Circulation 45 543 1972
94 Spagnuolo M Kloth H Taranta A Doyle E and Pasternack B Natural history of rheumatic aortic regurgitation Criteria predictive of death congestive heart failure and angina in young patients Circulation 44 368 1971
95 Shibata H., Matsuzaki T Hayashi, N Morishima A and Seino T Congenital heart disease in high school and college students Jpn Heart J 18 457 1877
96 Chen S C., Laks H Fagan L Tershluse D Kaiser G Barner H and Willman V L. Valve replacement in children Cardiovascular Surgery Suppl 2 Circulation 56 II 117 1977
97 John S Munsi S Sukumar I P and Cherian G Mitral valve replacement in children and adolescents with rheumatic heart disease Jpn Heart J 17 5 0 19 6
98 Davachi, F., Moller J H and Edwards, J E Diseases of the mitral valve in infancy Circulation 43 565 1971
99 Roberts W and Perloff J K A clinico pathologic survey of the conditions causing the mitral valve to function abnormally Ann Intern Med 77 939 19 2
100 Roberts W Anatomically isolated aortic valvular disease The case against its being of rheumatic etiology Am J Med 49 151 1970
101 Agner E Hannover L J and Leth A Yersinia enterocolitica carditis as a differential diagnosis—and the prognosis of the disease Scand J Rheumatol 7 26 19 8
102 Burch, G E Giles T D and Colcolough H L. Pathogenesis of "rheumatic" heart disease critique and theory Am Heart J 80 556 1970
103 Ward C Observations on the diagnosis of isolated rheumatic carditis, Am Heart J 91 545 19 6
104 Burch G E Sun S C Colcolough H L Sohal R S and DePasquale N P Coxsackie B viral myocarditis and valvulitis identified in routine autopsy specimens by immunofluorescent techniques Am Heart J 74 13 1967
105 Ward C Virus valvular heart disease Am Heart J 90 804 1975
106 Sun S C Sohal, R S Burch, G E Chu K C and Colcolough H L. Coxsackie virus B4 pancarditis in cynomolgus monkeys resembling rheumatic heart lesions, Br J Exp Pathol 48 655 1967
107 Sainani, G S Krompotic E and Slodki, S T Adult heart disease due to coxsackie B virus infection Medicine 47 135 1968
108 Okada R Glagov S and Lev M Relation of shunt flow and right ventricular pressure to heart valve structure in atrial septal defect Am Heart J 78 781 1969
109 Steinbrunn W., Cohn K and Selzer A Atrial septal defect associated with mitral stenosis The Lutembacher Syndrome revisited Am J Med. 218 293 1970
110 Barlow J B., Bosman C K., Pocock, W A. and Marchand P Late systolic murmurs and non ejection ("mid late") systolic clicks. An analysis of 90 patients, Br Heart J 30 203 1968
111 Rizzon P., Biasco G., Brindicci, G and Mauro F Familial syndrome of mid systolic click and late systolic murmur Br Heart J 35 245 1973
112 Barlow J B., and Pocock W A The problem of non-ejection systolic clicks and associated mitral systolic murmurs Emphasis on the billowing mitral leaflet syndrome Am Heart J 90 636 1975
113 Devereux R B., Perloff J K. Reichek, N., and Josephson M E Mitral valve prolapse Circulation 54 3 1976
114 Pocock W A., and Barlow J B Etiology and electrocardiographic features of the billowing posterior mitral leaflet syndrome Am J Med 51 731 1971
115 Steinfeld, L., Dimich I Rappaport, H., and Baron M Late systolic murmur of rheumatic mitral insufficiency Am J Cardiol 35 397 1975
116 Steinfeld, L., Yeh B C Baron M and Dimich, I The variability of mitral valve prolapse in rheumatic heart disease Circulation (Supp III) 49 and 50 III 208 1974
117 McLaren M J., Hawkins D M Lachmann A S Lakier J B Pocock W A., and Barlow J B Non ejection systolic clicks and mitral systolic murmurs in black school children of Soweto Johannesburg Br Heart J 38 718 19 6
118 Cohen M Pocock, W A., Lakier J B McLaren J M., Lachmann A S and Barlow J B Four year follow up of black school children with non-ejection systolic clicks and mitral systolic murmurs, Am Heart J 95 697 1978
119 Coombs, C Rheumatic heart disease Bristol, 1924 John Wright & Sons Ltd
120 Finlay D W Lucas, R H Lancet 2 420 1879
121 Massell, B F Fyler D C and Roy S B The clinical picture of rheumatic fever—Diagnosis immediate prognosis course and therapeutic implications, Am. J Cardiol. 1 436 1958
122 Feinstein A R Spagnuolo M., and Gill F A Rebound phenomena in acute rheumatic fever I Incidence and significance Yale J Biol Med 33 259 1961
123 Spagnuolo M and Feinstein A. R Rebound phenomena in acute rheumatic fever II Treatment and prevention Yale J Biol. Med 33 279 1961
124 Friedman S Harris T N., and Caddell, J L. Long term effects of ACTH and cortisone therapy in rheumatic fever Cardiologic observations on patients 5 to 8 years after hormone therapy in a controlled study J Pediatr 60 55 1962
125 Combined Rheumatic Fever Study Group A comparison of short term intensive prednisone and acetyl salicylic acid therapy in the treatment of acute rheumatic fever N Engl J Med 272 63 1965
126 Czoniczer G Amezcua F., Pelargonio S and Massell, B F Therapy of severe rheumatic carditis—Comparison of adrenocortical steroids and aspirin Circulation 29 813 1964
127 Taranta A Spagnuolo M and Feinstein A R Chronic" rheumatic fever Ann Intern. Med. 56 367 1962
128 Stollerman G H., Lewis, A J., Schultz, I., and Taranta A Relationship of immune response to group A streptococci to the course of acute chronic and recurrent

rheumatic fever Am J Med 20 163 1956
129 Wood H F Feinstein A R Taranta A Epstein J A and Simpson R Rheumatic fever in children and adolescents A long term epidemiologic study of subsequent prophylaxis streptococcal infections and clinical sequelae Ann Intern Med 60(Suppl 5) 31 1964
130 Taranta A and Gordis L The prevention of rheumatic fever Opportunities frustrations and challenges Cardiovasc Clin 4 1 1972
131 Gordis L Markowitz M and Lilienfeld A M The inaccuracy in using interviews to estimate patient reliability in taking medications at home Med Care 7 49 1969
132 Feinstein A R Wood H F Spagnuolo M Taranta A Tursky E and Kleinberg E Oral prophylaxis of recurrent rheumatic fever Sulfadiazine vs a double daily dose of penicillin J A M A 188 489 1964
133 Committee on Rheumatic Fever and Bacterial Endocarditis AHA Prevention of rheumatic fever Circulation 55 No 1 AHA Committee Report (ff p 222) 1019
134 Taranta A Fiedler J P Gilson B S Gordis L Hufnagel C A Klotz H H Markowitz M and Wannamaker L W Community resources for the management of patients with rheumatic heart disease Circulation 44 A 273 1971
135 Kaplan E L Dudding B A Top R H and Wannamaker L W Diagnosis of streptococcal pharyngitis Differentiation of active infection from the carrier state in the symptomatic child J Infect Dis 123 490 1971
136 Curran W J Glaucoma and streptococcal pharyngitis diagnostic practice and malpractice liability N Engl J Med 291 508 1974
137 Wannamaker L W A penicillin shot without culturing the child's throat J A M A 235 913 1976
138 Walsh B T Bookheim W W Johnson R C and Tompkins R K Recognition of streptococcal pharyngitis in adults Arch Intern Med 135 1493 1975
139 Tompkins R K Burnes D C and Cable W E An analysis of the cost effectiveness of pharyngitis management and acute rheumatic fever prevention Ann Intern Med 86 481 1977
140 Taranta A and Moody M Diagnosis of strepto[illegible] pharyngitis and rheumatic fever Symposium on la[illegible] tory diagnosis Pediatr Clin North Am 18 125 [illegible]
141 Kaplan E L Unresolved problems in diagnos[illegible] epidemiology of streptococcal infection *in* Strept[illegible] and streptococcal diseases recognition understa[illegible] and management ed. by Wannamaker L W [illegible] Matsen J M New York 1972 Academic Pre[illegible] 557 570
142 Taranta A Fiedler J Frank, C W Gilson, [illegible] Gordis L Hufnagel C Markowitz M and W[illegible] maker L W Prevention of rheumatic fever and [illegible] matic heart disease Circulation 41 A 1 1970
143 Catanzaro F J Rammelkamp C H Jr and C[illegible] vitz R Prevention of rheumatic fever by treatm[illegible] streptococcal infections. II Factors responsible f[illegible] ures N Engl J Med 259 51 1958
144 Bergman A B and Werner R J Failure of ch[illegible] to receive penicillin by mouth N Engl J [illegible] 268 1334 1963
145 Brink W R Rammelkamp C H Jr Denny [illegible] and Wannamaker L W Effect of penicillin and [illegible] mycin on the natural course of streptococcal to[illegible] and pharyngitis Am J Med 10 300 1951
146 Chamovitz R Catanzaro F J Stetson C A Rammelkamp C H Jr Prevention of rheumati[illegible] by treatment of previous infections I Evaluat[illegible] benzathine penicillin G N Engl J Med 2[illegible] 1954
147 Kaplan E L Bascom A F Bisno A Durack, [illegible] Houser H Prevention of bacterial endocarditis, [illegible] lation 56 1 AHA Committee Reports 139A 19[illegible]
148 Nakae M Murai T Kaneko Y and Mitsuha[illegible] Drug resistance in streptococcus pyogenes isol[illegible] Japan (1974 1975) Antimicrobial agents and [illegible] therapy Antimicrob Agents Chemother 12 42[illegible]
149 Beachey E H Chiang E Y Seyer J M Kang [illegible] Chiang T M and Stollerman G H Separation [illegible] type specific M protein from toxic cross reactiv[illegible] gens of group A streptococci Trans Assoc Am [illegible] cians 90 390 1977

Fundamentals of clinical cardiology

Mild mitral regurgitation and the mitral prolapse fiasco

Aubrey Leatham*
Wallace Brigden*
London England

The diagnosis prognosis and management of severe mitral regurgitation is comparatively well understood and its exact cause is usually clear Not surprisingly the diagnosis of slight mitral reflux its cause prognosis and management creates more difficulty and confusion though some of this appears to result from some ill considered statements and conclusions among the vast recent literature on the subject Indeed physicians may be puzzled by reading of chest pain dangerous dysrhythmias and sudden death as serious considerations in what otherwise appears to be a trivial lesion and even more puzzled by learning of the great frequency of mitral valve prolapse on the echocardiogram varying from 4 to 21% of the population[1, 2] These views are not in accord with our experience and continuing interest in this problem which extends over more than 25 years since we wrote on the subject in 1953[3] Indeed we hold the opinion that *isolated* disease of the mitral valve causing mild or moderate reflux seldom causes symptoms other than those of iatrogenic anxiety and that the prognosis for this lesion is good excepting the small risk of infective endocarditis and the very small one of progressive regurgitation usually as a result of chordal rupture These divergent opinions result in uncertainties about the problem which appear to have arisen because there has been an explosion of information brought about by advances in the tools of biological research and presented without due consideration of the cause of the mitral reflux and its natural history Furthermore there has been a tendency to take auscultatory and echocardiographic findings of reflux in isolation and to call these a syndrome—e g the late systolic murmur click syndrome the prolapse syndrome etc It is not always appreciated that the pattern of the systolic murmur of mild reflux whether late late crescendo or pansystolic is independent of the underlying pathology which may range from a deficit in the connective tissue or an inflammatory lesion of the valve to cardiomyopathy or coronary disease

It is interesting to recall that around the time of the first world war a mitral systolic murmur was considered to indicate serious valvar disorder carrying a grave prognosis reminiscent of some of the views aforementioned This misconception was countered by McKenzie and Lewis who stated that systolic murmurs were harmless in the absence of evidence of myocardial disease a statement nearer the truth than many made today about mitral valve prolapse

In 1953 the authors described 30 cases of isolated mitral reflux of varying severity diagnosed on the basis of a pansystolic murmur or late systolic murmur with or without a systolic click together with radiological evidence of systolic expansion and enlargement of the left atrium The diagnosis was confirmed at necropsy in nine cases and in only one was there histological evidence of rheumatic disease Even in the mild cases ventricular extrasystoles and a complaint of palpitations were found to be very common and the course was long and benign although it was occasionally interrupted by infective endocarditis and eventually by left ventricular failure in some It is of special interest that the systolic murmur always reached the aortic component of

From St. George's Hospital, National Heart Hospital and London Hospital, London England

Received for publication July 23 1979

Reprint requests Dr Aubrey Leatham 45 Wimpole St London W1M 7DG England.

* Physician, St. George's Hospital and National Heart Hospital.
† Physician London Hospital and National Heart Hospital.

0002-8703/80/050659 + 06$00.60/0 © 1980 The C V Mosby Co

the second sound that a late systolic crescendo to the pansystolic murmur was a common finding and that in some the murmur was confined to late systole as originally described by Griffith in 1882[5] and by Hall in 1903[6] and was preceded by clicks in two patients However around that time systolic clicks without a murmur or with a late systolic murmur were generally attributed to an exocardial origin (Gallavardin) They were dismissed as unimportant provided that the electrocardiogram was normal and that there was no other abnormality in the cardiovascular system—another thesis which was probably nearer the mark than some currently held

In 1961 Reid described eight cases with systolic clicks and in three the association with a murmur which reached the aortic component of the second sound suggested that these clicks arose in the chords of the mitral valve Barlow and associates in 1968 confirmed by ventriculography the conclusion reached by radiology and postmortem control that late systolic murmurs denoted mitral regurgitation and they showed that prolapse of the valve was the cause of the mitral regurgitation in some cases They published these findings in a series of patients with late systolic murmurs with or without systolic clicks but unfortunately they did not differentiate the causes of the slight mitral regurgitation which varied from isolated floppy or rheumatic mitral valves to cardiomyopathy and possibly ischemic fibrosis from coronary disease This series based entirely on the auscultatory findings resulted in the term Barlow s syndrome for any patient with a late systolic murmur with or without a click whatever the cause of the slight mitral regurgitation others have added to this rather confused picture Thus Perloff and colleagues[4] have stated that a late systolic murmur is the auscultatory hallmark of mitral valve prolapse it is of course the hallmark of slight or mild mitral regurgitation which is *sometimes* due to prolapse It was unfortunate that Barlow and co workers struck a note of alarm at the frequent association of ventricular ectopics with mitral reflux despite their previous description as frequent and unimportant in this condition while also reporting three sudden and unexpected deaths although not one of these was in their own series Two of these cases were relatives of a 17 year old boy with ECG strongly suggesting cardiomyopathy (Ref 8 Fig 8c) with its well known predisposition to sudden death the third case had been examined by a collea and the only portion of the ECG available showe T inversion in Lead II They concluded by stat that the prognosis of the syndrome is uncerta and sudden death may occur —a grave pr nouncement which has come to be too read associated with patients having a late systol murmur with or without a click whatever th pathogenesis of the valve lesion and whether not there is associated myocardial or conducti tissue disease The cases of sudden death report in the literature are few in number but are quote time and time again furthermore in every ca where we have been able to find a report on ECG, it was abnormal and often the QT inter was prolonged[1 9 14] Even the paper by Popp a co workers[15] which emphasized the frequency repolarization abnormalities of the ECG in cas of sudden death had the misleading title 'Life threatening arrhythmias in the mitral pr lapse syndrome Other factors associated wit death or dangerous dysrhythmias have be a low serum potassium or treatment with quin dine

Diagnosis

There are no specific symptoms Precord pains are frequent in patients with mitral refl and possibly more so when the cause is mitr valve prolapse Despite many statements to th contrary it is our view that these symptoms a rarely if ever of organic origin because the pa tern of pain is so variable often submammary a stabbing sharp or ill defined nature persistin for minutes hours or days and unrelated t effort although often to fatigue Indeed the symptoms are no different from those manifeste by other patients attending an outpatient cli with cardiac anxiety and no mitral regurgita tion Furthermore we are impressed by th absence of symptoms in those patients seen fo the first time who were unaware of the existen of disease Many patients with slight mitral regu gitation are the subject of anxiety enhanced b palpitation due to extrasystoles by extensiv investigations and by inadequate reassura There is certainly no resemblance of their pain to that of ischemic disease We remain totally unconvinced of a significant organic basis.

The clinical diagnosis of mitral regurgitation is essentially made by auscultation and is relatively easy provided that the relationship between th

apical systolic murmur and the aortic component of the second heart sound is clearly understood While the murmur of mitral regurgitation is invariably loudest at the apex and is often well heard into the axilla it may be mimicked in these respects by an aortic systolic murmur The mitral murmur however reaches and embraces the second aortic sound as expected from the relation between the left ventricular aortic and left atrial pressure pulses and it frequently has a crescendo in late systole whereas aortic systolic murmurs invariably finish before the aortic second sound Despite some statements to the contrary in our experience exceptions to this distinction between pansystolic regurgitant murmurs and mid systolic ejection murmurs have been very rare and are usually due to failure to identify the aortic component of the second sound which may be early [3]

When mitral regurgitation is slight from whatever cause the murmur is loudest in late systole but phonocardiograms often show small vibrations in early systole When however the murmur is preceded by a click early systole may be quite clear It seems probable that these systolic clicks even when occurring without a late murmur are often of chordal origin and it is probable (from echo evidence) that most are caused by a minimally floppy valve without regurgitation We have ventriculographic evidence to support this in two patients investigated for coincidental coronary disease and necropsy proof in one patient who died of carcinoma of the esophagus Difficulty arises when A_2 is soft or is drowned by the systolic murmur especially when left ventricular systole is shortened by mitral regurgitation and P_2 is mistaken for A_2 (particularly in severe mitral regurgitation) A similar problem arises when A is drowned by the murmur and stops before a loud third sound, but in both cases careful auscultation by inching with the stethoscope to the base of the heart should uncover A A carotid pulse recording or echocardiogram of aortic valve movement will identify aortic valve closure in difficult cases In calcific aortic stenosis the murmurs may be maximal at the apex and A may be inaudible making it impossible to decide the relationship between murmur and sound the slow rising arterial pulse then usually decides the issue Aortic systolic murmurs diminish greatly in intensity with premature beats causing diminution in stroke volume whereas mitral murmurs change little In mitral regurgitation due to prolapse the murmur is often louder in the standing position In obstructive cardiomyopathy there may be a loud apical to left sternal edge murmur and its crescendo is often later than in aortic stenosis although arising in the left ventricular ejection pathway Furthermore it may nearly reach A_2 making differentiation from mitral regurgitation very difficult a phonocardiogram will usually show the critical gap before A_2 The diagnostic difficulty in this disease may be compounded further by the presence of mitral reflux in addition to the obstructive problem but the murmur still stops before A_2 and becomes louder on the patient s rising from the squatting position

In mitral reflux the arterial pulse tends to be sharp rising and jerky depending on the degree of reflux Palpation of the apex may suggest a hyperkinetic hypervolemic ventricle depending on severity of the reflux and integrity of the muscle but in mild reflux both apical palpation and the pulse may be normal Ventricular extrasystoles are a common feature even with mild mitral reflux They appear to be of benign import long term follow up has shown no adverse mortality provided that the mitral regurgitation is not primarily due to coronary disease or to other serious myocardial disease

Critical examination of the electrocardiogram is most important in patients with evidence of mild mitral regurgitation for it may give the first important clue to the cause of the disorder A strictly normal graph apart from extrasystoles which are common enough in mild mitral prolapse is a strong pointer to primary valve disease However a clearly abnormal electrocardiogram indicates the presence of myocardial disease which may be the cause of the mild reflux or be associated with it or which may possibly result from it Gross abnormalities such as Q waves in inferior leads or the signs of severe myocardial hypertrophy are obvious indicators of serious myocardial disorder but the implications of lesser abnormality are often problematical Thus the cause of isolated T wave flattening or inversion in inferior leads is mostly obscure Such findings may be due to early muscle disease but on the other hand it is conceivable that they may be the result of prolonged abnormal tensions on the papillary muscles resulting from the dynamic disorder primarily arising in the valve

Echocardiography provides useful information both of valve movement and of myocardial disorder but erroneous interpretation and over diagnosis are problems and normal findings do not exclude mild degrees of defect in either valve or muscle Nevertheless correlation particularly in mitral valve prolapse with auscultation and angiography has shown the exceptional value of echocardiography in this field

Etiology

Mitral reflux may be due to disease which is primarily in the valve leaflets and chordae or secondary to local disease affecting the papillary muscles and adjacent myocardium or to generalized myocardial disease leading to so called functional regurgitation Primary valve lesions may produce reflux of any degree of severity Rheumatic fever continues to be the commonest cause of an inflammatory lesion of the valve but a prolapsing valve sometimes called a ballooning floppy or originally called a parachute valve, has superseded rheumatism as the commonest cause of isolated mitral reflux in Europe and North America The floppy valve shows an increasing prevalence with age affecting apparently 5% of the population over the age of 50 [14] and in a small number there is a familial incidence [16] Furthermore a similar valve abnormality occurs in some generalized connective tissue disorders such as Marfan s syndrome and Ehlers Danlos disease It has also been found in association with both types of atrial septal defect which is a special interest in that the lean asthenic habitus and high arched palate so often associated with A S D is reminiscent of the Marfan somatotype and a similar build is often found in subjects with an isolated floppy valve These associations together with the occasional familial incidence strongly suggest a genetically determined weakness of the connective tissue which under influence of wear and tear leads to a myxomatous transformation thus leading to cusp stretching and ballooning Other congenital lesions of the valve are relatively rare as are all forms of mitral reflux in infancy and childhood Clefts in the mitral valve occur as part of endocardial cushion defects and fenestrations of the valve may occur in isolation Inflammatory lesions of the valve may develop in patients who have one of the so called collagen diseases including systemic lupus polyarteritis nodosa and rheumatoid arthritis As in the case of the isolated floppy valve chordal rupture m occur in any one of these conditions

Secondary mitral regurgitation of all de with normal valves may arise in any of various forms of myocardial disease Mild regu tation is a common finding in patients who l recovered from inferior infarction—as shown late systolic murmur which incidentally we l never observed as a result of healed isol anterior infarction Mild regurgitation does appear to have a major adverse effect on pr sis in such cases Mitral regurgitation is com in hypertrophic cardiomyopathy where the m anism, though somewhat obscure also pro concerns abnormal papillary muscle functi

The recognition of the etiology of regurgi may be difficult A history of ischemic effor (cardiac pain) immediately points to cor artery disease with inferior ischemia or infa as the cause While a history of palp confirmed by the finding of multiple ventr ectopics was thought to be a feature of regurgitation in general it is probable th tendency is more frequent in patients wit dilated floppy valves though not necessaril much regurgitation which can perhaps a mechanical irritant Abnormalities of the e cardiogram favor myocardial disease or co disease but there are exceptions It n difficult to differentiate rheumatic from prolapsing valves With mild rheumatic regurgitation snaps and mitral diastoli murs even short ones are absent and e typical rheumatic thickening seen on the e diogram in severe cases may not be l Prolapse may be occasionally missed on th cardiogram

Prognosis

The apparently excellent prognosis of with primary mitral valve disease caus regurgitation can only be confirmed by lo follow up having regard to a variety of including etiology presence or absence rhythmia electrocardiographic abnormal echocardiographic findings unfortunat hard information is not available How one series of 62 patients with normal el diograms followed for nine to 22 year were no sudden deaths despite multiple lar extrasystoles in many Slowly incre gurgitation was not uncommon and cu

in one death in a patient 75 years old and there was unexpected chordal rupture in another subject necessitating valve replacement. Five patients developed infective endocarditis. In another series[11] all subjects had valvar prolapse but there was a wide range of dysfunction from none in patients with isolated systolic clicks to severe regurgitation in others. Not surprisingly, deterioration was found to be related to the degree of regurgitation but again the outlook was generally good; sudden death occurred in one patient known to have severe mitral regurgitation and another patient who had an episode of transient ventricular fibrillation had a grossly abnormal electrocardiogram.

In our experience, multiple ventricular extrasystoles do not seem to have an adverse influence on the prognosis unless associated with an abnormal electrocardiogram which shows abnormalities other than or in addition to the common finding of minor T wave abnormality in inferior leads. Similar conclusions were drawn from a monitored series. The outlook seems to be most uncertain in those rare cases where the electrocardiogram is abnormal with a prolonged QT interval with a family history of sudden death and perhaps in those cases where extrasystoles increase with exertion and fail to disappear at the height of exercise. In such cases the pathologist may find no evidence of myocardial abnormality. Whether the finding of mitral valve prolapse in such cases is a coincidence or whether it is linked in some way, possibly genetically, to a conduction abnormality resulting in electropathological disaster or whether ectopic beats become lethal under some special circumstances such as an electrolyte abnormality, remains unknown.

The prognosis in patients with mild mitral regurgitation which is secondary to myocardial disease, whether ischemic or otherwise, is almost wholly determined by the nature and severity of the myocardial disorder.

Management of slight mitral regurgitation

Since long term prognosis is very good except for the small risk of bacterial endocarditis, the only step that should be taken, apart from reassurance, is to advise antibiotic prophylaxis for dental extraction. Anxiety is a dominant feature in these subjects, particularly when frequent ectopics are a continual reminder of a valve lesion; the anxiety is often increased by unwise management and any other drug therapy should be avoided if possible. Even when there are myocardial abnormalities as suggested by an abnormal ECG, suppressant drugs for ectopic beats should be avoided if possible as they are often ineffective and the apparent need for them increases anxiety. Indeed, some may be dangerous, particularly in the presence of a long QT interval. Subjects with isolated systolic clicks and no regurgitant jet do not need antibiotic prophylaxis for dental extraction. Platelet emboli causing amaurosis fugax and other transient cerebrovascular disturbances may arise from floppy valves, but this is a relatively rare ocurrence. Antiprothrombin anticoagulants are not justified.

Conclusions

1. Isolated mild mitral regurgitation is a common disorder recognized by finding a crescendo systolic murmur which may be confined to late systole or continue throughout systole and in all cases up to the aortic second sound.

2. The commonest cause seems to be prolapse of the valve, sometimes suspected by finding a mid systolic click or clicks at the onset of the murmur, and readily confirmed by characteristic echocardiographic features in nearly all cases. This condition is probably due to the interplay of genetic and "wear and tear" factors leading to degeneration and stretching of valve cusps and chordae. Rheumatic disease may cause isolated mitral regurgitation without prolapse, but it is relatively uncommon without some stenosis as well.

3. Mild regurgitation is often secondary to myocardial disease—most commonly as a minor lesion after healed inferior infarction; it also occurs frequently in the cardiomyopathies. Dysfunction of the papillary muscles is probably the cause in most cases.

4. Symptoms from mild reflux are minimal and mostly due to anxiety—often precipitated by palpitations from extrasystoles. Precordial and submammary pain are common and are related to anxiety, but in some there may be true cardiac pain when the primary lesion is myocardial disease.

5. The prognosis of mild mitral regurgitation is generally good—dynamically the lesion is tolerated remarkably well. Ultimate prognosis, however, depends on the cause. Furthermore, a benign

Echocardiography provides useful information both of valve movement and of myocardial disorder but erroneous interpretation and over diagnosis are problems and normal findings do not exclude mild degrees of defect in either valve or muscle Nevertheless correlation particularly in mitral valve prolapse with auscultation and angiography has shown the exceptional value of echocardiography in this field

Etiology

Mitral reflux may be due to disease which is primarily in the valve leaflets and chordae or secondary to local disease affecting the papillary muscles and adjacent myocardium or to generalized myocardial disease leading to so called functional regurgitation Primary valve lesions may produce reflux of any degree of severity Rheumatic fever continues to be the commonest cause of an inflammatory lesion of the valve but a prolapsing valve sometimes called a ballooning floppy or originally called a parachute valve has superseded rheumatism as the commonest cause of isolated mitral reflux in Europe and North America The floppy valve shows an increasing prevalence with age affecting apparently 5% of the population over the age of 50 [14] and in a small number there is a familial incidence [15] Furthermore a similar valve abnormality occurs in some generalized connective tissue disorders such as Marfan s syndrome and Ehlers Danlos disease It has also been found in association with both types of atrial septal defect which is a special interest in that the lean asthenic habitus and high arched palate so often associated with A S D is reminiscent of the Marfan somatotype and a similar build is often found in subjects with an isolated floppy valve These associations together with the occasional familial incidence strongly suggest a genetically determined weakness of the connective tissue which under influence of wear and tear leads to a myxomatous transformation thus leading to cusp stretching and ballooning Other congenital lesions of the valve are relatively rare as are all forms of mitral reflux in infancy and childhood Clefts in the mitral valve occur as part of endocardial cushion defects and fenestrations of the valve may occur in isolation Inflammatory lesions of the valve may develop in patients who have one of the so called collagen diseases including systemic lupus polyarteritis nodosa and rheumatoid arthritis As in the case of the isolated floppy valve chordal rupture ma[illegible] occur in any one of these conditions

Secondary mitral regurgitation of all deg[illegible] with normal valves may arise in any of t[illegible] various forms of myocardial disease Mild regur[illegible] tation is a common finding in patients who ha[illegible] recovered from inferior infarction—as shown b[illegible] late systolic murmur which incidentally we ha[illegible] never observed as a result of healed isola[illegible] anterior infarction Mild regurgitation does [illegible] appear to have a major adverse effect on prog[illegible] sis in such cases Mitral regurgitation is comr[illegible] in hypertrophic cardiomyopathy where the me[illegible] anism though somewhat obscure also prob[illegible] concerns abnormal papillary muscle functio[illegible]

The recognition of the etiology of regurgita[illegible] may be difficult A history of ischemic effort [illegible] (cardiac pain) immediately points to coro[illegible] artery disease with inferior ischemia or infar[illegible] as the cause While a history of palpit[illegible] confirmed by the finding of multiple ventri[illegible] ectopics was thought to be a feature of m[illegible] regurgitation in general it is probable that[illegible] tendency is more frequent in patients with [illegible] dilated floppy valves though not necessarily [illegible] much regurgitation which can perhaps act[illegible] mechanical irritant Abnormalities of the el[illegible] cardiogram favor myocardial disease or cor[illegible] disease but there are exceptions It m[illegible] difficult to differentiate rheumatic from f[illegible] prolapsing valves With mild rheumatic [illegible] regurgitation snaps and mitral diastolic [illegible] murs even short ones are absent and ev[illegible] typical rheumatic thickening seen on the ec[illegible] diogram in severe cases may not be p[illegible] Prolapse may be occasionally missed on the[illegible] cardiogram

Prognosis

The apparently excellent prognosis of p[illegible] with primary mitral valve disease causin[illegible] regurgitation can only be confirmed by lon[illegible] follow up having regard to a variety of [illegible] including etiology presence or absence [illegible] rhythmia electrocardiographic abnormali[illegible] echocardiographic findings unfortunatel[illegible] hard information is not available Howe[illegible] one series of 62 patients with normal elec[illegible] diograms followed for nine to 22 years [illegible] were no sudden deaths despite multiple ve[illegible] lar extrasystoles in many Slowly increa[illegible] gurgitation was not uncommon and cul[illegible]

Clinical pharmacology of the new beta-adrenergic blocking drugs Part 13 The beta-adrenoceptor blocking drugs A perspective

William Frishman M D *
Bronx N Y

The introduction of beta adrenoceptor blocking drugs to the armamentarium of clinical medicine has provided one of the major therapeutic advances of this century The pioneers in this field hypothesized that beta adrenergic blockage would be beneficial in patients with angina pectoris this assumption has now been proven beyond doubt These pioneers could not have forseen the large spectrum of therapeutic indications that are now being discovered[1-60] (Table I) Beta adrenoceptor blocking agents have been found to be efficacious in neuropsychiatric disorders in endocrine disorders as well as in disorders of other organ systems (Table II) There is little doubt that the list of therapeutic indications in all the subspecialty areas of medicine will continue to lengthen as a result of the fecund inventiveness of clinical investigators At this juncture beta adrenoceptor blocking drugs have been approved by the United States Food and Drug Administration for the treatment of angina pectoris (propranolol timolol nadolol) hypertension (propranolol timolol nadolol metoprolol) arrhythmias (propranolol) migraine prophylaxis (propranolol) and glaucoma (timolol)

Within the next five years other beta adrenoceptor blocking agents with cardioselectivity partial agonist effects alpha adrenergic blocking activity and prolonged pharmacological half lives may be approved For the major cardiac indications (hypertension arrhythmias angina pectoris) no one beta adrenoceptor blocker has been shown to be more efficacious than another[61, 6] However the differing pharmacodynamic and pharmacokinetic properties of these drugs may reduce the incidence of certain adverse reactions and provide greater ease of administration Each compound must be measured to the needs of each patient with assessment of the benefit risk ratio This ratio must also take into account the financial impact of a given choice of drug to the potential benefit of that drug in an individual patient

The clinical observation that beta adrenoceptor blocking drugs are useful for so many different indications demonstrates the importance of the sympathetic nervous system in disease states and the role of the beta adrenoreceptors in multiple organ systems The molecular biology of the beta adrenoreceptor itself is being explored and this may shed light on the nature of pharmacological receptors and their activity

The beta adrenoreceptor changing concepts

Thirty years ago Ahlquist[63] performed detailed studies in which he thought to characterize the receptors by which catecholamines such as epinephrine and norepinephrine exert their physiologic effects His studies indicated that there were two major types of receptors alpha and beta adrenoreceptors Adrenergic receptors have since been subclassified into discrete $beta_1$ and $beta_2$[64] as well as $alpha$ and $alpha_2$[6] subtypes The recent development of radioligand labelling techniques have greatly aided the investigation of adrenergic receptors their molecular properties and their physiologic regulation

The older classical concept of adrenoreceptors

From the Division of Cardiology Department of Medicine Albert Einstein College of Medicine Bronx, N Y

Received for publication Jan 14 1980

Reprint requests William Frishman, M D Division of Cardiology Albert Einstein College of Medicine 1300 Morris Park Ave Bronx N Y 10461

Dr Frishman is a Teaching Scholar of the American Heart Association

000? 8 03/80/050665 + 06$00 60/0 © 1980 The C V Mosby Co

Table I Reported cardiovascular indications for beta adrenoceptor blocking drugs

1 Hypertension
2 Angina pectoris[3]
3 Arrhythmias [4]
4 Myocardial infarction [4]
5 Dissection of the aorta
6 Hypertrophic cardiomyopathy
7 Digitalis intoxication
8 Mitral valve prolapse
9 QT interval prolongation syndrome
10 Tetralogy of Fallot
11 Mitral stenosis
12 Cardiogenic shock
13 Fetal tachycardia
Neurocirculatory asthenia
Pulmonary stenosis and atresia
Erythromelalgia
Hypertensive response with endotracheal intubation
16 Hypertensive response with human coitus

Table II Reported non cardiovascular indicatio[ns] for beta adrenoceptor blocking drugs

Neuro psychiatric
1 Migraine[3]
2 Parkinson s disease[3]
3 Essential tremor[29]
4 Anxiety[30]
5 Exam nerves [3]
6 Alcohol withdrawal (delerium tremens)[32]
7 Narcotic withdrawal
8 Cocaine toxicity[34]
9 LSD Induced anxiety states[35]
10 Schizophrenia[36]
11 Lithium induced tremor[3]
12 Narcolepsy[3]

Endocrine
13 Thyrotoxicosis[39-40]
14 Hyperparathyroidism [4]
15 Insulinoma
16 Unstable juvenile diabetes mellitus[44]
17 Renal osteodystrophy[4]

Other
18 Glaucoma[46]
19 Tetanus
20 Acne vulgaris
21 Acute porphyria [5]
22 Endotoxin shock[50]
23 Hemorrhagic shock[5]
24 Ureteral colic[5]
25 Urinary incontinence[5]
26 Phantom Limb[54]
27 Bile acid induced diarrhea
28 Spastic colon[56]
29 Dysfunctional labor[5]
30 Hypothermia and hypoxia
31 Disseminated intravascular coagulation[59]
32 Oleander Poisoning[60]

as static entities in cells which simply serve to initiate the chain of events that lead to hormone action is no longer tenable The newer theory is that the adrenergic receptors are subject to a wide variety of controlling influences The result of these influences is to regulate dynamically the number of adrenergic receptors in tissues These changes in tissue concentration of receptor sites are likely involved in mediating important fluctuations in tissue sensitivity to drug action [66]

There are significant clinical and therapeutic implications of these new principles An apparent increase in the number of beta adrenoceptors and thereby a supersensitivity to agonists may be induced by chronic exposure to antagonists This phenomenon was described by Glaubiger and Lefkowitz [67] and may explain the propranolol withdrawal effect which occurs in patients with coronary artery disease upon sudden discontinuation of beta adrenoceptor blocking therapy [68] [69] With prolonged beta adrenoceptor blocker therapy receptor occupancy by catecholamines would be diminished and the number of available receptors is increased When the beta adrenoceptor blocker is suddenly withdrawn an increased pool of receptors would be open to endogenous catecholamines The resultant adrenergic stimulation may precipitate angina or myocardial infarction

The effects of thyroid hormone on adrenergic receptor numbers in experimental studies provide at least a partial explanation for therapeutic efficacy of beta adrenergic blo[ckers] in treatment of patients with thyrotoxic[osis] The receptor binding sites have been shown increased in hyperthyroidism[70] and decreas[ed in] hypothyroidism [71]

The number of beta adrenoceptors have been shown to increase with alcohol withdra[wal] which may explain the beneficial effects of [pro]pranolol for this indication [73]

The concentrations of β adrenoceptors i[n the] membrane of mononuclear cells signific[antly] decreases with age [74] This might explain the [pro]gressive resistance to β adrenoceptor bl[ocker] therapy reported with increasing age o[f]

hypertensive population As shown in a study of Buhler and associates[75] a good response to β adrenoceptor blocker therapy occurred in 90% of hypertensive patients in their twenties, but the percentage of responders fell progressively with increasing age[75]

An apparent decrease in beta adrenoceptor sites has been associated with the development of refractoriness or desensitization to endogenous catecholamines a phenomenon caused by the prolonged exposure of these adrenoceptors to high levels of catecholamines[76, 77] This desensitization phenomenon is not caused by a change in receptor formation or degradation but rather by catecholamine induced changes in the conformation of the receptor sites, thus rendering them ineffective These changes are reversible over a period of hours

β adrenoceptor blocking drugs do not induce desensitization or changes in the conformation of receptors. They do however block the ability of catecholamines to desensitize

The new information regarding adrenoreceptors has led to a better understanding of the physiological and pharmacological mechanisms that regulate their function These new concepts concerning adrenoreceptor function and regulation should also increase our understanding of agonist activity in disease states

The unresolved questions

In 1958 Powell and Slater[78] discovered dichloroisoprenaline (DCI) the first beta adrenoceptor blocker and for over 15 years beta adrenoceptor blocking drugs have been utilized in clinical medicine The efficacy of these agents in a multitude of clinical situations has been well demonstrated However there are many unanswered questions

1 It is not resolved how beta adrenoceptor receptor blockers reduce elevated blood pressure The postulated mechanisms include a reduction in cardiac output[7] an inhibition of renin secretion[80, 85] a reduction in plasma volume[86] a central neural effect[7, 88] a reduction of peripheral vascular resistance[89, 90] and a resetting of baroreceptor levels[1, 92] The resolution of this question may uncover the etiological mechanisms of essential hypertension

2. There is a disparity between the short pharmacokinetic half life of beta adrenoceptor blockers and the observed length of pharmacological effects.[93-96] Can beta adrenoceptor blockers be administered to patients in less frequent dosing regimens? Are metabolites important?[97]

3 Can the beneficial effects of beta adrenoceptor blockers in experimental myocardial infarction[98] be extrapolated to patients with acute myocardial infarction? Does chronic beta adrenoceptor blocker therapy provide prophylaxis against myocardial infarctions?[99] Do the anti platelet actions of some beta adrenoceptor drugs have clinical relevance in myocardial infarction prophylaxis?[100]

4 Do pharmacokinetic differences between beta adrenoceptor blockers[10] have clinical relevance? For example do drugs with increased lipid solubility and rapid uptake in neural tissue have specific advantages or disadvantages in therapy?

5 Do beta adrenoceptor blocking agents with alpha adrenergic blocking properties (labetalol)[0? 3] provide any advantage in therapy (i e., coronary spasm)?

6 The applications of beta adrenoceptor blocking drugs in a wide range of clinical situations suggest that sympatho-neuro adrenal imbalances may be an important etiological mechanism in disease The explanation of why beta adrenergic drugs work in such diverse clinical entities such as anxiety[30] acne vulgaris,[4] and porphyria[9] may provide insights into the mechanism of disease processes Perhaps the ancient Greek physicians were actually talking about sympatho adrenal alterations when they described the humors in balance[104] as a prerequisite to health

Conclusion and summary

The discovery of the alpha and beta adrenoceptor and the successful attempts to block these receptors have provided one of the most important scientific advances in clinical medicine The beta adrenoceptor blocking drugs have been shown to be efficacious for a host of cardiovascular and neuro-endocrine indications. The addition of beta blockers with varied pharmacodynamic and pharmacokinetic properties has not influenced therapeutic applications. However it has provided pharmacological alternatives when adverse reactions prohibit the use of a specific drug It has not been resolved whether the differences in lipid solubility or plasma half life have

any clinical relevance when using these drugs

The simple concept of competitive pharmacological inhibition at beta adrenoceptor sites has had revolutionary implications in human therapeutics Moreover, continued research efforts may further elucidate how the sympatho neuro adrenal function can influence disease states The pioneers in adrenoceptor research have left us with an unfinished puzzle It is our legacy, as the inheritors of the puzzle to fit all the pieces together so that the answers to the many unsolved questions can be known

R ERENCES

Prichard B N C and Gillam P M S The use of propranolol in the treatment of hypertension Br Med J 2 725 1964

Prichard B N C Propranolol as an antihypertensive agent AM HEART J 79 128 1970

3 Hamer J and Sowton E Effects of propranolol on exercise tolerance in angina pectoris Am J Cardiol 18 354 1966

4 Gillam P M S and Prichard B N C Propranolol in the therapy of angina pectoris Am J Cardiol 18 366 1966

5 Gibson D and Sowton E The use of beta adrenergic receptor blocking drugs in dysrhythmias Progr Cardio vasc Dis 12 16 1969

6 Jewitt D E Mercer C J and Schillingford J P Practolol in the treatment of cardiac dysrhythmias due to acute myocardial infarction Lancet 2 227 1969

7 Maroko P R and Braunwald E Modification of myocardial infarction size after coronary occlusion Ann Intern Med 79 720 1973

8 Frishman W H and Sonnenblick E H Propranolol therapy in acute myocardial infarction Cardiovasc Med 2 311 1977

9 Cohn J N Nitroprusside and dissecting aneurysms of aorta N Engl J Med 295 567 1976

10 Wheat M W Jr Treatment of dissecting aneurysms of the aorta current status Progr Cardiovasc Dis 16 87 1973

11 Cohen L S and Braunwald E Amelioration of angina pectoris in idiopathic hypertrophic subaortic stenosis with beta adrenergic blockade Circulation 35 847 1967

12 Sloman G Propranolol in management of muscular subaortic stenosis Br Heart J 29 783 1967

13 Turner J R B Propranolol in the treatment of digitalis-induced and digitalis resistant tachycardia Am J Cardiol 18 450 1966

14 Winkle R A Lopes M G Goodman D S Fitzgerald J W, Schroeder J S and Harrison D C Propranolol for patients with mitral valve prolapse AM HEART J 93 422 1977

15 Vincent G M, Abildskov J A and Burgess M J Q T interval syndromes Progr Cardiovasc Dis 16 523 1974

16 Shah P M and Kidd L Circulatory effects of propranolol in children with Fallot s tetralogy Observations with isoproterenol infusion exercise and crying Am J Cardiol 19 623 1967

17 Meister S G Engel T R Feitosa G S Helfant R H and Frankl W S Propranolol in mitral stenosis during sinus rhythm AM HEART J 94 685 197-

18 Bhatia M L Shrivastava S and Roy S G L diate haemodynamic effects of a beta adrenergic bl ing agent—propranolol—in mitral stenosis at fixed h rates Br Heart J 34 638 1972

19 Stubbs D Pugh D and Bell H Combined u isoproterenol and propranolol in cardiogenic sh Clin Pharmacol Ther 11 744 1970

20 Teuscher A Bossi E Imhof P Erb E Stocker l and Weber J W Effect of propranolol on fetal ta cardia in diabetic pregnancy Am J Cardiol 42 1978

21 Furberg C and Morsing C Adrenergic beta rec blockade in neurocirculatory asthenia Pharmaco Clinica 1 168 1969

22 Cumming G R and Mir G H Effects of propra on the resting and exercise hemodynamics of pulmo stenosis Can J Physiol Pharmacol 47 137 1969

23 Guntheroth W G and Kawabor I Tetrad of Fa in Heart Disease in Infants Children and Adolesc 2nd ed Moss A J Adams F H and Emmanoui G C eds Baltimore 1977 Williams & Wilkins Co ny pp 276 289

24 Bada J L Treatment of erythromegalia with pr nolol Lancet 2 412 1977

25 Oka Y Frishman W Becker R Kadish A Stro Matsumoto M Orkin L and Frater R Cli pharmacology of the new beta adrenergic bloc drugs Part 10 Beta adrenoceptor blockade and nary artery surgery AM HEART J 99 255 1980

26 Fox C A Reduction in the rise of systolic b pressure during human coitus by the beta adren blocking agent propranolol J Reprod Fertil 22 1970

27 Weber R B and Reinmuth O The treatmen migraine with propranolol Neurology 22 366 19-

28 Strang R R Clinical trial with a beta receptor an onist in Parkinsonism J Neurol Neurosurg Psych 28 404 1965

29 Murray T J Long term therapy of essential tr with propranolol Can Med Assoc J 115 892 19

30 Granville Grossman K L and Turner P The effe propranolol on anxiety Lancet 1 788 1966

31 Brewer C Beneficial effect of beta adrenergic bloc on exam nerves (Letter) Lancet 2 435 19-

32 Sellers E M Degani N C Silm D H and MacL S M Propranolol decreased noradrenaline secr and alcohol withdrawal Lancet 1 94 1976

33 Grosz H J Narcotic withdrawal symptoms in he users treated with propranolol Lancet 2 564 19-

34 Rapolt R T Gay G R and Inaba D S Propr lol a specific antagonist to cocaine Clin To 10 265 1977

35 Linken A Propranolol for LSD induced an states (Letter) Lancet 2 1039 1971

36 Yorkston N J Zaki S A Malik M K U Morr R C, and Havard C W H Propranolol in the co of schizophrenic symptoms, Br Med J 4 633, 19-

37 Kirk L Baastrup P C and Schou M Propra and lithium induced tremor (Letter) Lancet 1 1972

38 Kales A Soldatos C R Cadieux R Bixler E Tan T and Scharf M B Propranolol in the t ment of narcolepsy Ann Intern Med 93 41 19-

39 Das G and Krieger M Treatment of thyrot storm with intravenous administration of propra Ann Intern Med 70 985 1969

40 Lee T C, Coffey R J Mackin J Miranda Routon J and Canary J J The use of propranol

the surgical treatment of thyrotoxic patients, Ann Surg 177:643 1973
41 Caro J F., Castro J H., and Glennon J A Effect of long term propranolol administration on parathyroid hormone and calcium concentration in primary hyper parathyroidism Ann Intern Med 91 740 19 9
42 Fournier A., Coevoet B De Fremont J F Gueris, J Caillens, G Desplan, C., Calmette C and Moukhtar M S Propranolol therapy for secondary hyperpara thyroidism in uraemia Lancet 2 50 1978
43 Blum I., Aderka D Doron M., and Laron Z. Suppression of hypoglycemia by DL-propranolol in malig nant insulinoma (Letter) N Engl. J Med 299 487 19 8
44 Baker L., Barcai A Kaye R and Hague N Beta adrenergic blockade and juvenile diabetes acute studies and long term therapeutic trial. J Pediatr 75 19 1969
45 Caro J F Besarab A Burke J F., and Glennon J A A possible role for propranolol in the treatment of renal osteodystrophy Lancet 2 451 1978
46 *Zimmerman T., and Kaufman H Timolol a beta* adrenergic blocking agent for the treatment of glaucoma Arch. Ophthalmol. 95 601 1977
47 Prys-Roberts C Kerr J H Corbett J L. Crampton Smith A., and Spalding J M K Treatment of sympa thetic overactivity in tetanus Lancet 1 542 1969
48 Cunliff W J and Cotterill, J The effect of proprano lol on acne vulgaris and the rate of sebum excretion Br J Dermatol 83 550 1970
49 Douer D Weinberger A Pinkhas, J and Atsmon A Treatment of acute intermittent porphyria with large doses of propranolol J.A.M.A 240 766 1978
50 Berk J L., Hagen J F Beyer W H Gerber M J and Dochat G R The treatment of endotoxin shock by beta adrenergic blockade Ann Surg 169 74 1969
51 Berk, J L. Hagen J F Beyer W H Dochat G R and La Pointe R The treatment of hemorrhagic shock by beta adrenergic receptor blockade Surg Gynecol Obstet 125 311 1967
52 Kobacz G J The role of adrenergic blockade in the treatment of ureteral colic J Urol 107 949 1972
53 Khanna O M P Disorders of micturition Neurophar macologic basis and results of drug therapy Urology 8 316 19 6
54 Oille W A Beta adrenergic blockage and the phantom limb (Letter) Ann Intern Med 73 1044 1970
55 Coyne M J Bonorris G G Chung A Conley D and Schoenfield L J Propranolol inhibits bile acid and fatty acid stimulation of cyclic AMP in human colon Gastroenterology 73 971 1977
56 Lechin F Van Der Dijs B Bentolila A and Pena F The spastic colon syndrome therapeutic and pathophy siologic considerations J Clin Pharmacol 17 431 1977
57 Mitrani, A., Oettinger M Abinader E G and Sharf M Use of propranolol in dysfunctional labor Br J Obstet Gynecol 82 651 1975
58 Szerkeres L Papp J and Forster W The action of adrenergic beta receptor blocking agents on susceptibil ity to cardiac arrhythmias in hypothermia and hypoxia Experientia 21 720 1965
59 Moriau M Noel H and Masure R Effects of alpha and beta receptor stimulating and blocking agents on experimental disseminated intravascular coagulation Throm Diath Haemorr 32 15 1974
60 Szabuniewicz M McCrady J D and Camp B J Treatment of experimentally induced oleander poison ing Arch. Int Pharmacodyn Ther 189 12 1971
61 Thadani, U Davidson C., Singleton W and Taylor S *Comparison of the immediate effects of five beta* adrenoceptor blocking drugs in angina pectoris N Engl. J Med 300 750 1979
62 Frishman, W., and Silverman, R Clinical pharmacology of the new beta adrenergic blocking drugs. Part 3 Comparative clinical experience and new therapeutic applications, Am. Heart J 98 119 1979
63 Ahlquist R P A study of the adrenotropic receptors, Am. J Physiol. 153 586 1948
64 Lands, A. M., Arnold A., McAuliff J P., Ludena F P and Brown T G Jr Differentiation of receptor systems activated by sympathomimetic amines Nature 214 597 1967
65 Berthelsen S and Pettinger W A A functional basis for classification of α adrenergic receptors, Life Sci. 21 595 1977
66 Lefkowitz R J Direct binding sights of adrenergic receptors biochemical, physiologic and clinical impli cations. Ann Intern. Med. 91 450 1979
67 Glaubiger G., and Lefkowitz R. J Elevated beta adrenergic receptor number after chronic propranolol treatment Biochem Biophys. Res Commun 78 720 1977
68 Shand D G., and Wood, A. J J Propranolol with drawal syndrome—why? Circulation 58 202 1978
69 Alderman, E L., Coltart, D J Wettach, G E., and Harrison D C Coronary artery syndromes after sud den propranolol withdrawal, Ann Intern. Med. 81 625 1974
70 Williams, L T., Lefkowitz R. J., Watanabe A. M., Hathaway D R., and Besch, H R Jr Thyroid hormone regulation of β adrenergic receptor number J Biol. Chem 252 2787 1977
71 Banerjee S P., and Kung L S β adrenergic receptors in the rat heart effects of thyroidectomy Eur J Pharmacol. 43 207 1977
72 Banerjee S P Sharma, V K., and Khanna J M Alteration in β adrenergic receptor binding during etha nol withdrawal, Nature 276 407 1978
73 Sellers, E M., Degani, N C Salm D H., and MacLeod S M Propranolol-decreased noradrenaline secretion and alcohol withdrawal, Lancet 1:94 19 6
74 Schoken D D and Roth, G S Reduced β adrenergic receptor concentrations in aging man, Nature 267 856 1977
75 Buhler F R. Bukart F., Benno L E King M., Marbet, G and Pfisterer M Antihypertensive beta blocking action as related to renin and age A pharma cological tool to identify pathogenic mechanisms in essential hypertension, Am. J Cardiol. 36 653 1975
76 Lefkowitz R. J β adrenergic receptors recognition and regulation N Engl. J Med. 295 323 1976
77 Mukherjee C., and Lefkowitz R J Regulation of beta adrenergic receptors in isolated frog erythrocyte membranes Mol. Pharmacol. 13 291 1977
78 Powell C E., and Slater I H Blocking of inhibitory adrenergic receptors by a trichloro-analogue of isoproterenol J Pharmacol. Exp Ther 122 480 1958
79 Frohlich E D Tarazi, R. C., Dustan H P., and Page I H. The paradox of β adrenergic blockade in hyperten sion Circulation 37 417 1968
80 Michelakis, A. M., and McAllister R G *The effect of* chronic adrenergic receptor blockade on plasma renin activity in man J Clin Endocrinol. Metab 34 386 1972
81 Winer N., Chokshi, D S Yoom M S and Freedman, A. D Adrenergic receptor mediation of renin secretion, J Clin Endocrinol Metab 29 1168 1969

82 Buhler F R., Laragh J H., Baer J L. Vaughan E D Jr and Brunner H R Propranolol inhibition of renin secretion a specific approach to diagnosis and treatment of renin dependent hypertensive diseases N Engl J Med 287 1209 1972

83 Castenfors J Johnsson H and Oro L. Effect of alprenolol on blood pressure and plasma renin activity in hypertensive patients Acta Med Scand 193 189 1973

84 Zech P Y Labeeuw M., Pozet N Hadj Aissa A. Sassard J and McAnish J Response to atenolol in arterial hypertension in relation to renal function pharmacokinetics and renin activity Postgrad Med J 53 (Suppl 3) 134 1977

85 von Bahr C Collste P., Frisk Holmberg M Haglund K Jorfelt L. Orme M., Ostman J and Sjoquist F Plasma levels and effects of metoprolol on blood pressure adrenergic receptor blockade and plasma renin activity in essential hypertension Clin Pharmacol Ther 20 130 1976

86 Tarazi, R C Frolich, E D and Dustan H P Plasma volume changes with long term beta adrenergic blockade Am Heart J 82 720 1971

87 Dollery C T and Lewis P J Central hypotensive effect of propranolol Postgrad. Med. J 52 (Suppl. 4) 116 1976

88 Srivatsava R L. Kulshrestha V K. Singh, N and Bhargava K Central cardiovascular effect of extracerebroventricular propranolol Eur J Pharmacol. 21 222 1973

89 Atterhog J H Dunner H., and Pernow B Hemodynamic effect of long term treatment with pindolol in essential hypertension with special reference to resistance and capacitance vessels of the forearm Acta Med. Scand. 202 517 1977

90 Birkenhager W H DeLeeuw P W Wester A Kho T L. Vandongen R., and Falke H E Therapeutic effects of *β adrenoceptor blocking agents in hypertension in* Frick, P et al eds Advances in Internal Medicine and Pediatrics, Berlin 1977 Springer Verlag vol. 39 p 117

91 Prichard, B N C and Gillam P M S Treatment of hypertension with propranolol Br Med J 1 7 1969

92 Dunlop D and Shanks R G Inhibition of the carotid sinus reflex by chronic administration of propr[...] Br J Pharmacol. 36 132 1967

93 Berglund, G Andersson O Hansson, L., and Orla[...] R. Propranolol given twice daily in hypertension, [...] Med Scand 194 513 1973

94 Hansson L. Orlander R and Aberg H. Twice d[...] propranolol treatment of hypertension, Lancet 2 [...] 1971

95 Wilson M., Morgan, G., and Morgan T The effe[...] blood pressure of *β* adrenoreceptor blocking drugs g[...] once daily Clin Sci. Mol. Med. 51 59 s, 1976

96 Vedin A Wilhelmsson C., and Werko L. Com[...] tive study of alprenolol and methyldopa in previo[...] untreated hypertension Br Heart J 35 1285 19[...]

97 Frishman W Clinical pharmacology of the new b[...] adrenergic blocking drugs. Part 1 Pharmacod[...] and pharmacokinetic properties, Am Heart J 97 [...] 1979

98 Maroko P R and Braunwald E Modificatio[...] myocardial infarction size after coronary occlu[...] Ann Intern Med. 79 720 1973

99 Multicentre International Study *Improvement* [...] prognosis of myocardial infarction by long term b[...] adrenoceptor blockade using practolol, Br Med [...] 1 837 1976

100 Frishman W H., Weksler B., Christodoulou J S[...] en C., and Killip T Reversal of abnormal pla[...] aggregability and change in exercise toleran[...] patients with angina pectoris following oral propr[...] lol Circulation 50 887 1974

101 Johnsson G., and Regardh, C G Clinical pharma[...] netics of *β* adrenoreceptor blocking drugs Clin. P[...] macokin 1 233 1976

102 Farmer J B Kennedy I Levy G P and Marsha[...] J Pharmacology of AH 5158 a drug which blocks [...] alpha and *β* adrenoceptors Br J Pharmacol. 45 [...] 1972

103 Frishman W., and Halprin S Clinical pharmaco[...] of the new beta adrenergic blocking drugs. Part 7 [...] horizons in beta adrenoceptor blockade therapy [...] talol Am Heart J 98 660 1979

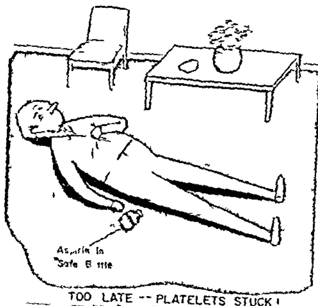
104 Lyons, A S and Petrucelli, R J *Medicine* New [...] 1976 Harry Abrams Inc p 251

Annotations

Of generic medicine bottles

The safety proprietary containers for medicine are so safe that no one can open them—neither children nor adults. The struggle to open them is so great and the frustration so exasperating that patients with angina pectoris precipitate an attack by merely trying to take a vasodilator (Fig 1) And old feeble chronically ill people cannot even "comply" with their doctor s instructions for medication—they are too feeble to open their safe" medicine bottles. So why even prescribe medicines? Patients cannot take them anyway I prescribed an antihypertensive for an old feeble lady patient but no one could "press and turn" the cap to open the bottle So frustrating and so futile were the attempts to open the bottle that we had to depend on diet and other measures for management instead of drugs. Maybe the pharmacist should be allowed to substitute an old fashioned generic bottle that patients can open in place of the new safe one

With regard to aspirin one has to match an arrow shaped nodule on the cap with a bead on the mouth of the bottle when attempting to open an aspirin bottle Once these markers are in line then with brute force the cap can be removed. But my cataract patients with diabetic neuropathy and without a sense of touch can never put these nodules together—so they must keep their fever or headache and must let their platelets stick" (Fig 1) The number of people who die of heart attacks trying to open their "safe" medicine bottles each year is probably greater than the number of children who have ever been poisoned by drugs in the entire history of America The deaths of these children are reported, but the incid nce of heart attacks caused" by the safe" medicine container is not—as far as I know Everyone must die—so sudden death from opening a patented nongeneric medicine bottle is better than dying of cancer and cancer chemotherapy I suppose It is much easier to "crack a safe in a bank than to open a safe bott e of aspirins Old people just have no chance! Who thought of the patented " proprietary safe and more expensive medicine bottles—the generic boys? We are strongly advised to have the proprietary containers



TOO LATE -- PLATELETS STUCK !

Fig 1

provided we dispense generic drugs in them to "save money Let it be lawful to dispense drugs the physician considers best and allow the pharmacist to substitute a cheaper "generic medicine container for a proprietary one so that patients even old feeble people who still want to live happily just a few years more can take their medicine Perhaps we can save many lives each year and extend the life expectancy of Americans with the use of generic medicine bottles.

G E Burch M.D
Tulane University School of Medicine and Charity Hospital of Louisiana
New Orleans La.

Adriamycin cardiotoxicity

The dose-limiting toxicities of anti cancer drugs are usually confined to tissues with a high mitotic rate such as bone marrow the gastrointestinal mucosa and hair follicles The anthracycline antibiotics daunomycin and doxorubicin (adriamycin) are exceptions to this rule Other anti neoplastic agents have been reported to cause mild chest pain and ECG changes (5 FU) or acute mild pericarditis when used in very larg single doses (cyclophosphamide) Only the anthracyclines consistently induce alterations in cardiac function which limit the safe cumulative dose of drug which can be given.

Anthracycline cardiotoxicity is an important problem for the practicing oncologist because these drugs cause regression of a variety of adult and pediatric neoplasms. Daunomycin and doxorubicin are included in the effective and probably curative regimens used to treat acute lymphatic leukemia of childhood Doxorubicin is a principal agent in the treatment of other leukemias, Hodgkins and non Hodgkins lymphomas

0002-8703/80/050671 + 04$00 40/0 © 1980 The C V Mosby Co

osteogenic sarcoma breast cancer ovarian carcinoma gastric cancer and oat cell carcinoma of the lung In addition adriamycin has been shown to have some activity in almost all adult tumor types except melanoma hypernephroma and colon cancer

There are two distinctly different types of cardiotoxicity associated with the use of these drugs First acute arrhythmias non specific ST T wave changes and even clinically inapparent decreases in left ventricular ejection fractions have been observed in 5 to 100% of patients studied.[5] These acute effects are always transient usually asymptomatic and do not require modification of the dose or schedule of doxorubicin administration except in a rare patient with a prior history of arrhythmias. The second and more serious cardiotoxicity is the late cardiomyopathy clinically indistinguishable from idiopathic or nutritional cardiomyopathies The congestive heart failure seen in these patients may be insidious in onset but frequently occurs abruptly as pulmonary edema precipitated by intravenous hydration associated with cancer therapy Heart failure usually develops within two months of the last dose of drug but instances of cardiomyopathy developing six months to almost a year later have been reported

The incidence (and probably the severity) of congestive heart failure is directly related to the cumulative dose of the drug Two percent of all patients given doxorubicin develop symptoms of congestive heart failure The incidence increases with increasing total dose to 3.5% of the patients given 400 mg/M, 7% of those given 550 mg/M and 15% of those who received 700 mg/M Most investigators have found that the incidence of cardiomyopathy is higher and the cumulative dose at onset of symptoms is lower in patients who receive mediastinal or left chest wall radiotherapy before with or after doxorubicin therapy Concurrent therapy with cyclophosphamide or prior heart disease do not clearly increase the risk of anthracycline cardiomyopathy

The earliest reports of doxorubicin induced heart failure suggested that it was untreatable and always fatal. Now that this is a well recognized complication of daunomycin or doxorubicin usage the drug is discontinued at the first sign of an unexplained tachycardia cough dyspnea or S gallop and the symptoms do respond to treatment with cardiac glycosides and diuretic therapy Recently it has been reported that children with documented pulmonary edema and cardiomegaly secondary to adriamycin may be asymptomatic without a cardiotonic regimen and with no echocardiographic evidence of left ventricular dysfunction more than one year after the onset of symptoms.

Histologically the cardiac lesions induced by anthracyclines are not distinctly different from those associated with many other cardiomyopathies but they can be readily distinguished from lesions resulting from radiotherapy or arterial occlusion Initially the damage is focal and scattered throughout the heart. With larger doses of adriamycin the heart is diffusely involved. The most frequent manifestations of anthracycline damage are myofibrillar lysis and cytoplasmic vacuolization Fibrosis as typically seen after radiation damage occurs much less frequently and there is no inflammatory response

Since no more than 30% of patients have developed congestive heart failure even when quite large doses of [illegible] are given it seemed plausible at one time [illegible] was considerable variation in patients [illegible]

rubicin cardiotoxicity This has been studied in a number of animal models of doxorubicin cardiomyopathy Although some species seem to be less sensitive to the drug than others all species evaluated have shown evidence of cardiac damage after doxorubicin therapy Within each species the range of cumulative drug dose at which lesions become apparent is small, and in rabbits at least the damage is progressive after the drug is discontinued Morphologic abnormalities of heart muscle have been found in monkeys after a single dose of the drug Cardiac biopsies of the hearts of patients given doxorubicin show typical lesions in almost all patients given [illegible] mg/M or more of the drug However it is not clearly established that the lesion is progressive in man after the drug has been stopped in one group of patients no abnormalities were seen one year after they had received 450 mg/M or more total dose of doxorubicin At the present time one would have to conclude that all patients have cardiac damage when treated with daunomycin or doxorubicin and that all patients will become symptomatic from a cardiomyopathy if sufficient drug is given

The pathophysiology of this cardiotoxicity is poorly understood The anti tumor activity of the drug is thought to be related to its intercalation with DNA Since other anti-tumor drugs with a similar mechanism of action do not cause cardiomyopathy it seems unlikely that intercalation is an adequate explanation of the unique cardiotoxicity associated with the anthracyclines The hearts of rabbits treated with doxorubicin have abnormally high tissue levels of calcium and it has been proposed that adriamycin induced [illegible] changes are due to a calcium mediated necrosis. However attempts at preventing the cardiotoxicity using chelating agents in animal models have been unsuccessful. Adriamycin has a glycosidic structure and specifically inhibits sodium potassium activated ATP ase This suggests that the doxorubicin effect might occur at the same site as digitalis toxicity or that a common receptor for the anthracyclines and the cardiac glycosides might be necessary for uptake of these drugs into the heart Currently available data suggest that strophanthin will not block doxorubicin uptake in animal models and there are insufficient data to justify clinical trials using pretreatment with digitalis compounds. In a recently reported study of doxorubicin cardiotoxicity in rabbits histamine and catecholamine-blocking agents used together seemed to prevent the appearance of a cardiomyopathy This suggests another possible mechanism that might explain both the acute and chronic effects of doxorubicin on the heart

Doxorubicin also inhibits Co Q (Ubiquinone) enzyme systems in isolated mitochondria and the administration of Ubiquinone to rabbits or rats has been found to at least partially block some of doxorubicin s cardiotoxicity However Ubiquinone is also a free radical scavenger Recent data have been reported which strongly suggest that doxorubicin cardiotoxicity and possibly even the anthracycline anti-tumor effect is mediated either through the production of superoxides or by activation of the anthracyclines to a free radical state It has been shown in mice that lipid peroxidation and acute histologic changes in murine heart muscle are prevented by pretreatment with α tocopherol, another free radical scavenger No convincing data have yet been reported to suggest that Ubiquinone or α tocopherol can be used to either decrease the incidence of heart failure

ncrease the cumulative doses of drug which can be safely administered to patients

Other methods used to ameliorate the cardiotoxicity of adriamycin include (1) the use of a weekly rather than a 3 week interval between drug doses The more frequent administration of smaller doses appears to decrease the incidence of heart failure but clearly does not eliminate heart damage. (?) Promising analogues of doxorubicin have been developed, some of which have decreased cardiac toxicity when used in animal systems Several of these drugs have now entered clinical trial[14]

A number of noninvasive tests and parameters of left ventricular function have been used to monitor patients receiving adriamycin therapy These include systolic time intervals derived from phonocardiograms and ejection fractions determined from echocardiograms[??] All of these studies demonstrate a deterioration of left ventricular function in groups of patients given increasingly large cumulative doses of the drug None of these tests have proven valuable in predicting that a patient will develop a cardiomyopathy far enough in advance of symptoms to allow much adjustment of dru dosage[10]

Up to one third of patients may have transient or permanent abnormalities in systolic time intervals or ejection fractions before cumulative doses of 500 mg/M have been given. Congestive heart failure in these patients is uncommon *and the routine use of such studies* may *encourage the* physician to prematurely and inappropriately discontinue chemotherapy in many patients. It has been suggested that the cumulative dose limit might be cautiously raised beyond 500 mg./M in some patients if serial studies are obtained before each dose of the drug is given This also has not proved possible since patients with perfectly normal studies have developed pulmonary edema within 1 to 2 months of their last normal study and their last dose of adriamycin [10]

Recently a study utilizing ejection fractions derived from first pass radionu lide angiography purported to show that this test was more specific than the use of phonocardiograms or echocardiograms. It is not clear why this should be so since the doxorubicin lesion is diffuse and there is no reason to expect that left ventricular wall motion will not be uniform This approach needs confirmation with a larger group of patients in a direct comparison with echocardiography

The most specific evaluation of cardiotoxicity is that of the Stanford group using endomyocardial biopsy They have devised a semi quantitative scoring system The mean score increases in patients given cumulative doses from 45 to 545 mg./M In the Stanford studies these biopsies are performed in outpatients and the morbidity is low The test has the advantage of providing information independent of changes in left ventricular function which are dependent upon both the doxorubicin affect and the work load placed on the heart Because of the invasiveness of this approach it has not been used extensively in other centers Further it is still not clear whether a low or negative score is meaningful at an early stage when lesions are focal and scattered At present endomyocardial biopsy is the most specific way to determine anthracycline cardiotoxicity short of clinically apparent heart failure It is probably the most useful tool available to evaluate anthracycline analogues in man

Doxorubicin is likely to continue to be a major component of oncologic regimens until there are agents which specifically block doxorubicin cardiotoxicity or analogues which are equally efficacious with no cardiotoxicity At present a cumulative dose limit of 450 to 500 mg/M should be observed except in the infrequent patient in whom the threat of disease and the benefit of further doxorubicin therapy clearly outweigh the threat of heart failure The routine use of serial noninvasive tudies of left ventricular function are not of proved value in decreasing the incidence of doxorubicin induced cardiomyopathy

I Craig Henderson M.D
Emil Frei III M.D
Harvard Medical School
Sidney Farber Cancer Institute
44 Binney St
Boston Mass 02115

REFERENCES

1 Stevenson D L. Mikhailidis, D P., and Gillett D S Cardiotoxicity of 5 fluorouracil, Lancet 2 406 1977
2 Appelbaum F R., Strauchen J A Graw R G., Jr., Savage D D Kent, K M Ferrans V J and Herzig G P Acute lethal carditis caused by high-dose combination chemotherapy A unique clinical and pathological entity Lancet 1 58 19 6
3 Blum R. H An overview of tudies with adriamycin (NSC1?3127) in the United States Cancer Chemother Rep 6 247 1975
4 George S L Aur R J A Mayer A. M., and Simone J V A reappraisal of the results of stopping therapy in childhood leukemia N Engl J Med 300 ?69 1979
5 Minow R A Benjamin R. S and Gottlieb J A Adriamycin (NSC123127) cardiomyopathy—an overview with determination of risk factors, Cancer Chemother Rep 6 195 1975
6 Singer J W Narahara K A Ritchie J L Hamilton G W and Kennedy J W Time and dose-dependent changes in ejection fraction determined by radionuclide angiography after anthracycline therapy Cancer Treat Rep 62 945 1978
7 Van Hoff D D Rozencweig M., Layard M Slavik M and Muggia F M Daunomycin induced cardiotoxicity in children and adults, Am. J Med. 62 200 1977
8 Von Hoff D D Layard M., Basa P Davis H L., Von Hoff A. L. Rozencweig M. and Muggia F M Risk factors for doxorubicin induced congestive heart failure Ann Intern. Med 91 710 1979
9 Balcerzak S P Christakis J Lewis, R P Olson H M. and MaLpeis L. Systolic time intervals in monitoring adriamycin induced cardiotoxicity Cancer Treat. Rep 62 893 1978
10 Bristow M. R Mason J W., Billingham M E and Daniels, J R Doxorubicin cardiomyopathy evaluation by phonocardiography endomyocardial biopsy and cardiac catheterization Ann Intern Med 88 168 1978
11 Goorin, A., Borow K., Goldman A Williams, R., Henderson, I C., Jaffe N., Cohen H., and Sallan S Natural history in children of congestive heart failure (CHF) secondary to adriamycin (ADR) cardiomyopathy (CM) Proc Am Assoc Cancer Res. Am. Soc Clin Oncol. 20 3_8 1979
12 Billingham M E., Mason, J W Bristow M R and Daniels, J R Anthracycline cardiomyopathy monitored by morphologic changes, Cancer Treat. Rep 62 865 1978
13 Young D M Pathologic effects of adriamycin (NSC

123127) in experimental systems Cancer Chemother Rep 6 1,9 1975
14 Jaenke R S Delayed and progressive myocardial lesions after adriamycin administration in the rabbit Cancer Res 36 2958 1976
15 Benjamin R S Eewer M S MacKay B Ali M K Legha S S and Valdivieso M An endomyocardial biopsy study of anthracycline induced cardiomyopathy—detection reversibility and potential amelioration Proc Am Assoc Cancer Res Am Soc Clin Oncol 20 372 1979
16 Olson H M Young D M Prieur D J LeRoy A F and Reagan R L Electrolyte and morphologic alterations of myocardium in adriamycin treated rabbits Am J Pathol 77 439 1974
17 Bristow M R and Billingham M E Personal communication
18 Gosalvez M Van Rossum C D V and Blanco M F Inhibition of sodium potassium activated adenosine 5 triphosphatase and ion transport by adriamycin Cancer Res 39 257 1979
19 Bachur N R Reiter W and Arena E Cardiac uptake of adriamycin (NSC 123127) not affected by strophanthin G (NSC 25485) Cancer Chemother Rep 59 765 1975
20 Bristow M R Billingham M E and Daniels J R Histamine and catecholamines mediate adriamycin cardiotoxicity Proc Am Assoc Cancer Res Am Soc Clin Oncol 20 118 1979
21 Iwamoto Y Hansen I L Porter T H and Folkers K Inhibition of coenzyme Q enzymes succinoxidase and NADH oxidase by adriamycin and other quinones having antitumor activity Biochem Biophys Res Commun 58 633 1974
22 Folkers K Choe J Y and Combs A B Rescue by coenzyme Q from electrocardiographic abnormalities caused by the toxicity of adriamycin in the rat Proc Natl Acad Sci 75 5178 1978
23 Bachur N R Gordon S L and Gee M V A general mechanism for microsomal activation of quinone anticancer agents to free radicals, Cancer Res 38 1 [illegible] 1978
24 Myers C E McGuire W P Liss R H Ifrim I Grotzinger K and Young R C Adriamycin The role of lipid peroxidation in cardiac toxicity and tumor response Science 197 165 1977
25 Weiss A J and Manthel R W Experience with the use of adriamycin in combination with other anticancer agents using a weekly schedule with particular reference to lack of cardiac toxicity Cancer 40 2046 1977
26 Henderson I C Billingham M Israel M Krishan A and E Frei III Comparative cardiotoxicity studies of adriamycin (ADR) and AD 32 in rabbits Proc Am Assoc Cancer Res Am Soc Clin Oncol 19 158, 1978
27 Benjamin R S Mason J W., and Billingham, M E Cardiac toxicity of adriamycin complex and rubidazone evaluation by electrocardiogram and endomyocardial biopsy Cancer Treat Rep 62 935 1978
28 Ewy G A Jones S F Friedman, M J Gaines J and Cruze D Noninvasive cardiac evaluation of patients receiving adriamycin Cancer Treat Rep 62 915 1978
29 Ramos A Meyer R A., Korfiagen J Wong K Y and Kaplan S Echocardiographic evaluation of adriamycin cardiotoxicity in children, Cancer Treat Rep 60 1[illegible] 1976
30 Henderson I C Sloss L J., Jaffe N Blum R H, and Frei E III Serial studies of cardiac function in patients receiving adriamycin Cancer Treat Rep 62 923, 1978
31 Alexander J Dainiak N Berger H J Goldman L Johnstone D Reduto L Duffy T Schwartz P Gottschalk A and Zaret B L Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiography N Engl J Med 300 269 1979

Vascular permeability factor and nephrotic syndrome*

The nephrotic syndrome consists of a disturbance of glomerular permeability resulting in albuminuria hypoalbuminemia and edema. In childhood the majority of cases respond to corticosteroid therapy and have only minimal histological changes in the glomeruli evident on light microscopy A number of clinical observations have suggested an immuno pathogenesis of the steroid responsive nephrotic syndrome relapse following infection association with atopy and response to desensitization association with Hodgkin s disease association with HLA B12 response to corticosteroids and alkylating agents and response to measles and measles vaccine A number of these observations suggest that minimal change nephropathy is produced by a systemic abnormality of T lymphocyte function resulting in the release of a circulating chemical mediator toxic to the glomerular basement membrane The lack of evidence of a humoral antibody response induced by measles which modifies cell mediated immunity and the therapeutic benefits of steroids and cyclophosphamide which abate cell mediated responses support this hypothesis

Lymphocytes may be divided by their responses into two broad groups, thymus dependent (T) cells which are prominent in the delayed hypersensitivity reaction and antibody secreting (B) cells In vivo these cell populations are interdependent T-cells mediate the antibody response pattern of B-cells to antigen T and B-cells act together with other cells (i.e macrophages and polymorphs) in producing immunological effects However the pathogenesis of a given disease may depend more heavily on either T or B-cell activity

When T lymphocytes are stimulated specifically with antigen they elaborate a variety of soluble factors termed lymphokines

*The author was supported by a grant from the National Kidney Research Fund of Great Britain

-ines which display different biological activities. One of these the skin reactive factor has been extensively studied in guinea pigs. This factor induces a rapid increase in vascular permeability at the inter dermal site of injection Using the Evans Blue technique Lagrue and associates demonstrated that stimulated peripheral lymphocytes from nephrotic patients produced a soluble factor that increases the vascular permeability of guinea pig skin and proteinuria on injection in the renal artery of a rat They presented pharmacological evidence suggesting that the lymphokine activated the Kinin system

Boulton-Jones and Simpson have recently demonstrated that lymphocytes from patients with minimal change nephropathy produce abnormal amounts of vascular permeability factor during relapse even in the absence of an in vitro stimulant, postulating that they have already been stimulated in vitro Couser and colleagues were unable to detect differences in vascular permeability factor between nephrotic patients and controls We have also been unsuccessful in attempting to demonstrate a lymphokine effect released by lymphocytes of nephrotic children in relapse of their disease prior to treatment with corticosteroids

The data presented to date on this aspect of lymphocyte function in the nephrotic syndrome are intriguing but do not present a coherent picture and the suggestion that the syndrome results from a disorder to T-cell function remains speculative

Richard S Trompeter M.B M.R C P
Lecturer in Paediatrics
Guy s Hospital
London SE1 9RT
England

REFERENCES

1 Thomson P D Barratt T M., Stokes C R Turner M W and Soothill, J F HLA antigens and atopic features in steroid responsive nephrotic syndrome of childhood, Lancet 2 765 1976
2. Hardwicke J P., Soothill, J F Squire J R and Holti, G Nephrotic syndrome with pollen hypersensitivity Lancet 1 500 1959
3 Moorthy A V Zimmerman S W., and Burkholder P M Nephrotic syndrome in Hodgkin s disease evidence for pathogenesis alternative to immune complex deposition, Am J Med 61 471 1976
4 Janeway C A Moll, G H Armstrong S H Wallace W M Hallman N and Barness, L A Diuresis in children with nephrosis. Comparison of response to injection of normal human serum albumin and to infection particularly measles, Trans. Assoc A Physicians 61 108 1948
5 Yuceoglu A M., Bercovicz S and Chiu J Effect of live measles vaccine on childhood nephrosis, J Pediatr 74 291 1969
6 Salhoub R. J Pathogenesis of lipoid nephrosis a disorder of T-cell function Lancet 2 556 1974
7 Pick E Krejcki, J., Cech, K., and Turk, J L Interaction between sensitized lymphocytes and antigen in vitro 1 The release of a skin reactive factor Immunology 17 741 1969
8 Maillard J L Pick, E and Turk, J L Interaction between sensitized lymphocytes and antigen in vitro V Vascular permeability induced skin reactive factor Int Arch. Allergy 42 50 1972
9 Lagrue G Xheneumont S Branellec A., Hirbec G., and Weil, B A vascular permeability factor elaborated from lymphocytes. 1 Demonstration in patients with nephrotic syndrome Biomedicine 23 37 1975
10 Lagrue G Xheneumont S., Branellec A., and Weil, B Lymphokines and nephrotic syndrome Lancet 1 271 1975
11 Lagrue G Brannellec A. Blanc C., Xheneumont S Beaudoux C., Sobel A., and Weil, B A vascular permeability factor in lymphocyte culture supernatants from patients with nephrotic syndrome II Pharmacological and physicochemical properties Biomedicine 23 73 1975
12 Boulton-Jones, M., and Simpson S Release of vascular permeability factor from lymphocytes of patients with minimal change nephropathy 105th Annual General Meeting London 1979 Abstract Renal Association.
13 Couser W Badger A., Cooperbrand S., Stilmant M., Jermanovich, N., Aurora S Doner D., and Schmitt, G Hodgkin s disease and lipoid nephrosis Lancet 1 912 1977
14 Trompeter R S Barratt, T M and Layward, L. Vascular permeability factor and nephrotic syndrome, Lancet 2 900 1978

Cardiopulmonary bypass and postoperative neurologic dysfunction

The reported incidence of neuropsychiatric dysfunction following open heart surgery and cardiopulmonary bypass (CPB) is variable Javid and associates reported that while 53% of patients undergoing CPB sustained a transient disorder of neurologic function only 14% had residual cerebral deficit at the time of discharge Branthwaite[3] noted a significant alteration in cerebral electrical activity during cardiopulmonary bypass in 63% of patients, but only 8% (10 of 140) had any postoperative neurologic damage Lee and co workers observed neither neuropsychiatric complications nor mortality in a group of patients undergoing cardiac reparative" surgery without CPB However patients exposed to extracorporeal circulation sustained an incidence of 23% neurologic deficit and 14% psychiatric deficit Further in the CPB group the mortality rate was three times higher in the subgroup of patients who had sustained neuropsychiatric deficit Similar results were observed in our surgical intensive care unit Patients who exhibited psychiatric dysfunction postoperative-

Table I Risk factors for the development of postoperative neuropsychiatric dysfunction*

Patient
- Age
- Cerebrovascular disease
- Neurologic disease
- *Cardiac disease—*
  - Type
  - Severity
  - Duration

Operative
- Hypotension (BP < 50 mm Hg)
- Blood transfusion
- Hypoxia
- Hypocapnia

Cardiopulmonary bypass
- Duration
  - Flow
  - Pressure (BP < 50 mm Hg)
  - Blood volume
- Emboli—gas, particulate matter microemboli, fat emboli
- Hypoxia
- Hypocapnia
- Oxygenator
- Temperature
- Hematocrit

Postoperative
- Hemodynamic
- Metabolic
- Environmental

*Reproduced from Barash, P G et al Assessment of cerebral function during cardiopulmonary bypass Heart & Lung 8 280 1979

ly were at higher risk for mortality (31%) than the control population (12%) and required three times the length of stay

Risk factors for central nervous system (CNS) dysfunction can be related to the patient s pre-existing disease as well as to the specific perioperative experience anesthesia surgery cardiopulmonary bypass, and postoperative period (Table I) Of these variables those related to the patient are probably the most significant Age (> 50 years) and the presence of pre existing neurologic or cerebrovascular disease increases the risk of postoperative deficit Using non invasive evaluation Diethrich and colleagues reported that 50% of patients (mean age = 63 years) scheduled for elective open heart surgery had significant cerebrovascular abnormalities requiring further preoperative diagnostic evaluation by invasive methods In five patients carotid endarterectomy was performed prior to or simultaneous with their cardiac surgery Th duration sever ity and type of cardiac disease ar ther important patient factors Valvular heart disease [illegible] at an even higher risk CNS damage following valve [illegible] ement [illegible] 2 times greater than that compared to [illegible] heart surgery without valve replacement

Of the operative risk factors [illegible] is probably the most important [illegible]

employed may affect postoperative neurologic function. Carlson and associates demonstrated that a membrane oxygenator resulted in improved visual motor testing when compared to a bubble oxygenator At the onset of CPB a number of pathophysiologic changes occur In addition to the institution of non pulsatile flow changes in cerebral venous pressure, hemoglobin (dilutional anemia) concentration of intravenous or inhalational agents temperature (hypothermia) and arterial oxygen and carbon dioxide tensions can be observed. These are capable of causing marked alteration in the regulation of cerebrovascular activity During CPB maintaining adequate tissue perfusion by optimal perfusion pressure and flow must be assured Stockard and co-workers reported that six out of seven patients who sustained prolonged hypotension during CPB had significant postoperative neurological deficits. They concluded that (1) during CPB a mean blood pressure of 50 mm Hg was critical and in elderly patients with cerebrovascular disease that a perfusion pressure of [illegible] mm Hg may be required (2) risk and severity of deficit are related to the degree and duration of hypotension (3) CNS morbidity could be prevented by the use of vasopressor agents when hypotension occurs The duration of CPB also contributes to neurologic morbidity Prolonged perfusion pressures (greater than 120 to 180 minutes) are associated with a two to threefold increase in neurologic deficits

Microembolization to the brain during CPB has been previously hypothesized to be a major cause of neuropsychiatric dysfunction Aguilar and associates found fat emboli in 78% of autopsied cases Non fat emboli (fibrin calcium striated muscles platelet and fibrin aggregates) were found only when perfusion exceeded 90 minutes. With the introduction of microfilters into the CPB circuit a marked decrease in neurologic deficit has been noted The use of Dacron filter reduced the incidence of cerebral non fat emboli from 31% to 4% which was associated with a reduction in hospital mortality rate from 20% to [illegible]%

Monitoring of CNS function during open heart surgery is crucial Evaluation of the patient with a thorough neurologic history and examination is mandatory However during the surgical procedure the neurologic examination may be of limited value General anesthetics muscle relaxants, and other ancillary medications (atropine trimetaphan catecholamines etc) can obscure or camouflage signs of CNS damage Occasionally pupillary signs may demonstrate a focal neurological deficit In addition sinus arrhythmia or bradycardia may herald the elevation of intracranial pressure However these are relatively nonspecific may be related entirely to intrinsic cardiovascular pathology and when present occur late in the development of intracranial compression.

Direct monitoring of CNS function includes measurements of electrical activity metabolism blood flow and intracranial pressure The current "gold standard for measurement of electrical activity is the electroencephalogram (EEG) Although EEG monitoring provides valuable data it is not universally employed during open heart surgery and CPB The noisy electrical environment of the operating room can obscure the recording of minute voltages. The recordings are voluminous and do not readily lend themselves to interpretation and trending In many cases a special technician is required to operate the electroencephalograph and to collect data Unfortunately postoperative neurological deficits occasionally result even with a normal EEG during cardiopul

nonary bypass. However persistence of the asymmetrical EEG abnormality is most commonly associated with a unilateral postoperative neurologic deficit

As a result newer techniques have evolved to overcome these disadvantages. Power spectral analysis of the EEG has been advanced as a means to overcome the aforementioned liabilities and yet capitalize on the advantages of conventional EEG monitoring. In order to simplify the evaluation of intraoperative EEG tracings, computer programs have been written to provide a compressed spectrum analysis of the EEG as recorded on line and displayed graphically with an XY plotter. A sudden shift in the dominant frequencies is readily visible even to the untrained observer. Stockard and coworkers have demonstrated that power spectrum analysis of EEG activity provides a readily recognizable pattern of change when cerebral perfusion is inadequate during cardiopulmonary bypass. A close correlation was observed between the appearance and persistence of power spectrum EEG changes and the occurrence of postoperative neurologic deficit

Direct metabolic measurements of cerebral function e g cerebral venous oxygen tension via the internal jugular bulb have had very limited clinical application. However the mixed venous oxygen tension (P O) has been widely used as a measure of the adequacy of whole body tissue perfusion during CPB. The P O represents the balance between oxygen delivery and utilization at the tissue level. Although normal P O doesn t ensure adequate cerebral perfusion low P O can be indicative of poor tissue perfusion in general, including the brain

Measurement of intracranial pressure is an important advance in the management of patients with acute CNS dysfunction. However the patient undergoing open heart surgery is anticoagulated during CPB and thus this important neurodiagnostic technique is contraindicated.

A significant number of patients sustain some form of neuropsychiatric dysfunction following cardiopulmonary bypass. The factors that place the patient at greatest risk are advanced age presence of cerebrovascular or neurologic disease and the duration of cardiopulmonary bypass. At present our routine clinical monitoring is relatively insensitive to early detection of neurologic dysfunction. The EEG or its variants seem to be the best direct monitor of cerebral function. This is analogous to monitoring hemodynamic performance by using only the electrocardiogram. Newer methods utilizing computer analysis and the EEG have great potential

Paul G Barash M D
Associate Professor of Anesthesiology
Director Surgical Intensive Care Unit
Dept of Anesthesiology
Yale University School of Medicine
333 Cedar St
New Haven Conn 06510

REFERENCES

1 Barash P G Katz J Kopriva C J Shaffer W B and Kitahata L M Assessment of cerebral function during cardiopulmonary bypass Heart Lung 8 280 1979
2 Javid H Tufo H M, Najafi H, Dye W S Hunter J A, and Julian O C Neurologic abnormalities following open heart surgery J Thorac Cardiovasc Surg 58 502 1969
3 Branthwaite M A Detection of neurological abnormalities following open heart surgery Thorax 28 464 1973
4 Lee W H Brady M P, Rowe J M, and Miller W C Effects of extracorporeal circulation upon behavior personality and brain function Part II Hemodynamic metabolic and psychometric correlation Ann Surg 173 1013 1971
5 Hale M Koss, N Kerstein M Camp K and Barash P Psychiatric complications in a surgical ICU Crit Care Med 5 199 1977
6 Branthwaite M A. Neurological damage related to open heart surgery Thorax 27 948 1972
7 Diethrich E B Reiling M Ibrahim F and Koopot R Stroke screening prior to coronary artery bypass. Cardiovascular diseases, Bull Texas Heart Inst 4 262 1977
8 Carlson R G Lande A J Landis B Rargoz B, Baxter J, Patterson R H, Stenzel K, and Lillehei C W The Lande-Edwards membrane oxygenator during heart surgery J Thorac Cardiovasc Surg 66 894 1973
9 Stockard J J Bickford R G and Schauble J F Pressure dependent cerebral ischemia during cardiopulmonary bypass, Neurology 23 521 1973
10 Aguilar M J Gerbode F and Hill, J D Neuropathologic complications of cardiac surgery J Thorac Cardiovasc Surg 61 6 6 1971
11 Hill, J D Osborn J J Swank R L Aguilar M J Lanerolle P and Gerbode F Experience using a new Dacron wool filter during extracorporeal circulation Arch. Surg 101 649 1970
12 McDowall D G Monitoring the brain Anesthesiology 45 117 1976
13 Witoszka M M Tamura H Indeglia R Hopkins, R W and Simeone F A Electroencephalographic changes and cerebral complications in open heart surgery J Thorac Cardiovasc Surg 66 855 1973
14 Myers R R Stockard J J Fleming C J, and Bickford R G The use of online telephonic computer analysis of the EEG in anesthesia Br J Anaesth 45 644 1973
15 Stockard J J Bickford R G, Myers R R Hund M H Dilley R B and Schauble J F Hypotension induced changes in cerebral function during cardiac surgery Stroke 5 730 1974
16 Stanley T H and Isern Amaral J Periodic analysis of mixed venous oxygen tension to monitor the adequacy of perfusion during and after cardiopulmonary bypass, Can. Anaesth. Soc J 21 454 1974

Applicability of correcting the QT interval for heart rate

To the Editor

Correcting the QT interval for heart rate (QTc) is a common and well established practice It is assumed the QT interval consistently shortens as heart rate increases based on studies by Bazett by Fridericia[2] by Simonson and associates, and by others Many of these studies contain experimental bias that limit evaluation of the QT interval changes e g analysis of heart rate/QT variation was *between* individuals rather than *within* individuals

The present questions arose from a critical electrocardiographic review that was part of a study that evaluated the cardiovascular pulmonary and neuromuscular effects of an experimental bronchodilator (clenbuterol) in 11 patients with reversible obstructive airways disease Each subject had 48 measurements of QT interval following both adrenergic drugs or placebo Three dosage strengths of the new bronchodilator were compared to two of a standard (terbutaline) and a placebo QT intervals were measured and rounded to 10 msec intervals while heart rates were obtained from R R intervals and were rounded to even beats per minute Data were analyzed by analysis of variance and linear regression

Dose related increases in heart rate were observed following administration of each bronchodilator and after a meal. Analysis of variance revealed residual changes in QTc following correction by the formula of Bazett No residual changes were observed using either of the correction formulas of Simonson and colleagues This suggests the latter formula was a better corrector of QT for heart rate than the more commonly used square root of the R R interval formula of Bazett

The present data were tested further by QT interval versus heart rate regression analysis which revealed an inverse relationship (Fig 1) similar to the log linear formula of Simonson and associates While the population data agree line C there was a disparate relationship in some individuals—lines A and B *Individual B* showed marked changes in the QT interval at nearly the same heart rate and *individual A* demonstrated an invariant QT with marked heart rate changes The coefficient of determination (r^2) representing the entire population demonstrates the same thing i e 75% of the variation in QT is not explained by heart rate Therefore population statistics such as those of Simonson and coworkers, as well as ours may be inappropriate when applied to a specific ECG While this has been recognized by Simonson and associates and by others it is not generally appreciated

The misapplication of statistical inference to a cardiac pharmacologic decision based on a prolonged QTc would be misleading in instances where the patient s QT varies widely at the same heart rate or is invariant as heart rate changes Thus, rate correcting an individual s QT interval is appropriate when known rate related QT changes are present

Carl V Manion M D
Thomas L Whitsett M D
Michael F Wilson M D

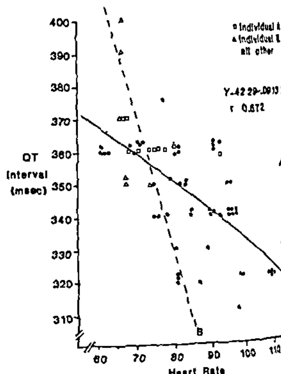


Fig 1 A plot of all the QT intervals and heart rate values Regression coefficients for individual A (*squares*) and individual B (*triangles*) represent the extremes in variance from those of the entire group s (*C*) The linear regression constants for the formula Y = A – Bx are shown

Department of Med
University of Oklahoma Health Sciences Center College of Medicine
Oklahoma City VA Medical Center
Oklahoma City Okla

REFERENCES

1 Bazett H C An analysis of the time-relations of electrocardiograms Heart 7 353 1920
2 Fridericia L A Die Systolendauer im Elektrokardiogram bei normalen Menschen und bei Herzkranken, Med. Scand 53 489 1920
3 Simonson E Cady L D Jr and Woodbury M normal Q T interval Am Heart J 63 47 1962

Improved circulation by coronary bypass?

To the Editor

I would like to say just a few words concerning Annotation by Dr Burch in a recent issue of the Journal (September 1979 Vol. 98 404) entitled "Of 'The quality life "

Improvement of the circulation of the blood into the myocardium after bypass surgery has not been positively proved Dr Burch and I agree that the quality of life may have been improved but its longevity is not changed

How can it be otherwise? If we inject sap into the branches of a tree will this act improve the circulation and the color of the leaves in the fall? Surely not

I think the same is true for the human heart. Good distal run-off for the coronary tree cannot exist when there are atheromatous plaques in the coronary arteries. I have seen ECGs unchanged after bypass surgery and I am not surprised at this I hope nevertheless, that investigations will continue particularly as regards scanning at rest and after exercise both before and after bypass surgery

I am reasonably certain that greater success will come from the improvement of eating habits and from the use of medications to diminish cholesterol, triglycerides, etc

All of this is just to emphasize that I agree wholeheartedly with Dr Burch s Annotation

Dr Jean Marie Laporte
Clinique Medicale de l Est
30 Est Blvd St Joseph
Montreal H2T 1G9 Quebec Canada

Reduction of QRS amplitudes after cardiac dilatation

To the Editor

Lekven and associates reported recently in this JOURNAL on some very interesting ECG findings during acute dilatation of the left and right ventricles in dogs Recording both from endocardial and epicardial electrodes they found consistently a decrease of unipolar QRS potentials with every increment in ventricular size which was induced by blood infusion under pressure End-diastolic volume and pressure were carefully monitored during the experiments and a linear relationship between ventricular size and QRS amplitude decreases could be established.

Similar findings were reported from body surface leads by Ishikawa and co workers in 1971 They found QRS voltage increases in the body surface ECG when cardiac size decreased and QRS voltage decreased in patients exhibiting progressive cardiac dilatation in congestive heart failure These relatively consistent clinical observations have now been confirmed in a more direct way by the very thorough study of Lekven and associates It has always surprised us that very little clinical use is being made of such simple observations since chest x rays and ECGs are readily available in practically all hospitalized patients Such QRS voltage changes are frequently interpreted erroneously as increases or decreases in left ventricular hypertrophy (LVH) when changes in cardiac size provide a much more plausible explanation

QRS voltage decreases due to cardiac dilatation have been a puzzling phenomenon for many years and a number of hypotheses have been developed Lekven and colleagues assume that stretching and thinning of the ventricular wall may play a role in the observed QRS decreases. Other investigators have tried to reconcile the findings with the Brody effect which is based on increases or decreases of the intracavitary blood mass Radial electromotive forces are expected to increase and tangential forces to decrease when the ventricular blood volume becomes larger In the left ventricle activation has usually been assumed to be predominantly radial. This should lead to QRS increases in dilatated hearts, which is contrary to actual observations More recent studies by Roberts Hersh, and Scher[4] may be quite pertinent in explaining some of the contradictory findings. They found substantially more rapid excitation parallel to the long axis of cardiac fibers than perpendicular to them Tissue resistivity was at the same time lower parallel to the fibers by a factor of 3.2 Their results suggest a preferential spread of activation along cardiac fibers. Since the majority of the fibers have an orientation which is more or less parallel to the endocardial and epicardial surfaces one must also assume a predominantly tangential spread of activation If this is the case Brody s postulates could be reconciled with both Ishikawa s and Lekven s findings

Hubert V Pipberger M.D
VA Medical Center and
Department of Clinical Engineering
and Medicine George Washington University
Washington D C

REFERENCES

1 Lekven J Chatterjee K., Tyberg J V and Parmley W W Reduction in ventricular endocardial and epicardial potentials during acute increments in left ventricular dimensions, AM HEART J 98 200 1979
2. Ishikawa K., Berson A S., and Pipberger H V Electrocardiographic changes due to cardiac enlargement, AM HEART J 81 635 1971
3 Brody D A. A theoretical analysis of intra cavitary blood mass influence on the heart lead relationship Circulation 4 731 1956
4 Roberts D E Hersh, L. T., and Scher A M Influence of cardiac fiber orientation on wavefront voltage conduction velocity and tissue resistivity in the dog Circ Res 44 701 1979

Lyle s maneuver—an overdue critique

To the Editor

Widespread acceptance of unproved diagnostic procedures is not rare in the history of medicine It therefore does not come as a surprise that a recent editorial purports that the value of Lyle s maneuver (respiratory variation) is to differentiate benign from pathological Q waves in electrocardiographic (ECG) Lead 3 Lyle is often said to have observed that inspiration caused a Q wave in Lead 3 (Q_3) to diminish or disappear among normal subjects and to persist among patients with inferior myocardial infarction (IMI) Lyle herself in presenting this data however actually stated we have not been able to gather enough cases to prove anything statistically but we believe that the cases shown illustrate certain fundamental principles "[2] Such anecdotal experiences are sometimes seized upon and propagated by many over time as having diagnostic value without adequate data evaluation A survey of 166 upper Midwestern hospitals published some time ago revealed that approximately one-third of these

institutions routinely employed respiratory cycle evaluation of Lead 3 of the standard ECG

At least two well designed studies within the past few years have cast serious doubt upon the value of Lyle s maneuver Shettigar and colleagues retrospectively studied 48 patients with IMI confirmed by at least two of the following findings (1) a clinical history of acute myocardial infarction with classical ECG evolution (2) greater than 80% narrowing of the right coronary artery on coronary angiography and (3) significant inferior wall asynergy during contrast ventriculography A full 20% of these patients revealed significant diminution or disappearance of Q waves in ECG Lead 3 with full inspiration[5]

A prospective study to evaluate Lyle s maneuver in 33 patients with IMI (classical serial ECG changes as well as positive cardiac enzyme elevations including MB CK) and in 22 normal healthy volunteers less than 30 years of age was recently reported Utilizing the vectorcardiogram (VCG) these authors demonstrated that approximately one half of patients with documented IMI as well as one half of normal controls with Q had an "inferior shift in their initial 20 to 30 msec vector An analysis of the standard ECG revealed a diminution of Q_3 wave depth in 61% (20 out of 33) of IMI patients and only 12% (one out of eight) of normals—results directly opposed to those predicted by Lyle[3] Again quoting Lyle directly concerning patients with Q and no history of myocardial infarction, she stated that in some cases we have been unable to make Q disappear or to lower R_L by inspiration so that its failure to disappear an equivocal observation "[3]

Certainly these recent data would suggest that maneuver when applied to a given individual, will diagnostic information in the majority of cases and times be dangerously misleading

Michael J Zema
Dept. of M
Director of Car
Brookhaven Memorial Hospital Medical
101 Brookhaven Hos
Patchogue N Y

REFERENCES

1 Ferrer M I Respiratory maneuvers in electro graphic diagnosis, Chest 73 445 19 8
2 Mimbs J W., de Mello V and Roberts R. The respiration on normal and abnormal Q wave HEART J 94 579 1977
3 Lyle A M Further observations on the deep Q electrocardiogram AM HEART J 28 199 1944
4 Berman R and Simonson E Survey of electro graphic practices in the Upper Midwest Lancet 1960
5 Shettigar U R Hultgren H N., Pfeifer J Lipton M J Diagnostic value of Q waves in myocardial infarction AM HEART J 88 170 19

Book reviews

Coronary Heart Disease in Young Women Edited by M F Oliver M D London & New York 1978 Churchill Livingstone 26? pages. Price $?3 50

This publication contains papers presented at a symposium on Coronary Heart Disease in Young Women The presentations are interesting and extremely good The subject of the symposium is rather unusual for symposia on arteriosclerosis Surely the answers desired are still not available but the questions and answers clearly display the opinions of the participants and are certainly thought provoking The reader who is actively engaged in the practice of cardiology and research and who follows the current and even the older literature will find nothing new in this publication Nevertheless he will find the book easy to read interesting and a good review of current concepts of the causes of arteriosclerosis and its appearance in early life as well as in young women

The Merck Manual—13th Edition By Robert Berkow M D Editor and John H Talbot M D., Consulting Editor Rahway New Jersey 1977 Merck Sharp & Dohme Research Laboratories, 2165 pages

The Merck Manual is a classic among publications in medicine Several hundred thousand are purchased each year The Bible is the only publication which, on a regular basis, outsells this manual. The book contains a wealth of practical clinical information in general medicine Every physician will find this to be an indispensable reference manual It is impossible to review each subject in detail but suffice it to say that it is well indexed clearly written and published extremely well The first edition appeared in 1899 and the manual has continued to improve since Each edition is better than the preceding one and of course it is always as current as any publication of this type could be This is an excellent and valuable reference book on general medicine for students housestaff and practicing doctors

Advances in Cardiology vol 24 Cardiac Rehabilitation Edited by K Konig Waldkirch and H Denolin Basel, Switzerland 1977 S Karger A G Medical and Scientific Publisher 201 pages Price $53 50

Cardiac rehabilitation is important in cardiac therapy Physicians fail to realize their responsibility in this aspect of management of the cardiac patient Cardiac rehabilitation is both overstressed as well as under considered. This book includes discussions of evaluation of cardiovascular functions from the point of view of exercise testing electrocardiography therapeutic principles psychological aspects of rehabilitation and therapeutic results and future cardiac considerations This is a good book for internists, cardiologists and trainees. This reviewer is impressed with the lack of emphasis by physicians in clinical study of the value of the patient s ordinary daily physical and psychic responses to everyday stress rather than on hazardous and expensive treadmill exercise testing etc in the evaluation of cardiovascular function After all, patients walk climb stairs, mow their lawns mend things at home keep house etc under daily living conditions These are stressful activities Why not learn how well they function at home and at work at any given time prior to and after myocardial infarction with therapy and follow up evaluation? Patients do not live on treadmills and they never will And there is a training factor in treadmill and other exercise studies The doctor must know his patient in order to "rehabilitate" him Physicians can learn a great deal about patients with careful history taking Nevertheless this book is interesting and clearly reveals the trends in the practice of cardiology in some centers of the world and contains a great deal of interesting and useful information

Primary and Secondary Angina Pectoris By Maseri, Klassen, and Lesch New York 1978 Grune & Stratton, Inc 470 pages Price $22.50

This book is a publication of the proceedings of an international symposium held in Pisa Italy during June 1976. The book is divided into nine chapters each containing several papers The subjects discussed include experimental studies of coronary blood flow obstructive coronary artery disease coronary spasm ("primary" angina) prognosis therapy and suggestions for future investigations The emphasis on coronary spasm is evident throughout the publication. The concept of spasm of the coronary arteries in episodes of angina pectoris is certainly an old concept However the use of coronary angiography in patients which reveals coronary arterial constriction during attacks" of angina has stimulated greater interest in the role of spasm Many catheterization laboratory groups have noted the relationship of coronary artery spasm to the syndrome of angina pectoris. This publication is a good one which properly indicates the importance of not losing sight of spasms of the coronary arteries when considering the disease in patients The contributors to the symposium were quite numerous The book is highly recommended to all physicians

Books received

Computer Techniques in Cardiology Volume 4 Edited by Lee D Cady Jr New York, 1979 Marcel Dekker Inc 480 pages Price $45 00

Dynamic Electrocardiographic Recording By Gerald F Fletcher M D New York, 1979 Futura Publishing Company 170 pages Price $19 50

Biology of Brain Tumors Edited by O D Laerum D D Bigner and M F Rajewsky Geneva, 1978 International Union Against Cancer 209 pages. Price 15 Swiss francs

Venenkrankheiten/Peripheral Venous Disorders By Leo K Widmer Bern Switzerland 1978 Hans Huber Publishers 9? pages

Stress By Tom Cox, Baltimore 1978 University Park Press, 200 pages Price $12.95

Eighth Biennial Cardiology Symposium

The Johns Hopkins Medical Institutions will present an eighth biennial cardiology symposium entitled A Review of Current Problems in Diagnosis and Therapy to be held from June 5 through 7 1980 in Baltimore This two and one-half day course is designed for the general internist family physician and the practicing cardiologist Frequently encountered problems in the diagnosis and management of cardiovascular diseases will be emphasized The symposium is approved for 18 Category I AMA credit hours the fee is $150 00 For further information, contact Program Coordinator The Johns Hopkins University Turner Auditorium 720 Rutland Ave Baltimore Md 21?05 Telephone (301) 955 5880

Cardiology 80

The Seventh Annual Intensive Coronary Care Symposium entitled "Cardiology 80" will be presented on June 15 through 17 1980 at the Harbour Castle Hilton Hotel, Toronto Ontario Canada The symposium is sponsored by the Health Sciences Division Humber College Rexdale Ontario Fees for the symposium proper are $80 with an additional fee of $55 for those wishing to attend a pre-symposium one-day workshop Twelve credit hours will be awarded by Humber College toward one course in the Certificate in Clinical Nursing additional credits may be awarded pending approval. For further information contact Conference & Seminar Services, Humber College ?05 Humber College Blvd Rexdale Ontario M9W 5L7 Canada Telephone (416) 675-3111 ext 539 or 540

Workshop on Heart Attack Prevention

The University of Minnesota Medical School is offering a workshop on the prevention of heart attacks entitled Practical Guides to Risk Factor Reduction " to be held on June 2 through 4 1980 at Spring Hill Center Minneapolis. For more information contact Lori Wheatcroft, Office of Continuing Medical Education University of Minnesota Medical School Box 293 Mayo Memorial Bldg 420 Delaware Street S.E. Minneapolis Minn 55455

World Congress of Pediatric Cardiology

The World Congress of Pediatric Cardiology will be held at the Wembley Conference Centre London on June 2 through 6 1980 Congress officers will be Dr J E Edwards, Minneapolis Dr A S Nadas Boston Professor G Brom, Leiden, and Professor Fergus Macartney London The scientific program will comprise invited lectures by outstanding international authorities there will also be seminars and free communications The program aims to cover all aspects of pediatric cardiology pediatric cardiac surgery and related disciplines For further information contact Secretary General, Professor Fergus Macartney World Congress of Paediatric Cardiology The Hospital for Sick Children Great Ormond St London WC1 3JH England

American Heart Journal

June 1980 Volume 99 Number 6

Editorial

Beta adrenoceptor blockade in acute myocardial infarction

R M Norris M D FRCP FRACP

Auckland New Zealand

The severity of myocardial infarction depends mainly on a critical balance between oxygen supply and demand for a portion of the myocardium which may vary in size from a few grams to 40% or more of the mass of the left ventricle This in turn is determined principally by the size of the supply territory of the coronary vessel which is narrowed or occluded and the adequacy of the collateral circulation Experimental studies suggest that myocardial ischemia progresses irreversibly to infarction if the period of myocardial oxygen and substrate deprivation is prolonged beyond 4 to 6 hours If coronary blood flow is restored after 3 hours however some of the ischemic tissue does not undergo necrosis

That the anatomical lesions in the coronary circulation are not the sole determinant of infarct size has however been shown by a large body of experimental evidence from this it appears that infarct size after a standardized arterial ligation can be modified by early intervention Of all the many interventions which are possible beta adrenoceptor blockade is perhaps the most physiologically attractive [5] It has been known for many years that enhanced sympathetic activity follows myocardial infarction that levels of circulating epinephrine and norepinephrine are raised and that these hormones increase oxygen demand for the myocardium by stimulation of the cardiac beta adrenoceptors

From the Co n ry Care Un t G een Lan Hospital Auckland New Zealand

Recei ed f publication March 19 1979

Reprint req ests R M Norris, M D Cor ary C re Un t, Gree Lane Hospital, Green Lane West, A ckland 3 New Zeal nd

Although beta blocking drugs have been used successfully from the time of their introduction for reversal of the imbalance between oxygen supply and demand in angina pectoris [9] the history of their use in clinical myocardial infarction has been much less straightforward This is mainly because early clinical trials ignored the short time span during which pathophysiological changes of infarction can be modified as well as the clinical pharmacology of propranolol absorption and metabolism by the liver Moreover they did not consider the possibility that a beneficial effect of beta blockers on infarct size might happen in treated patients in the absence of a demonstrable reduction in acute mortality rate Thus although propranolol in a dose of 40 to 80 mg daily did not reduce mortality rate in four well controlled randomized trials failure *could be explained by the fact that intervention* was too little and too late adequate blood levels of propranolol were almost certainly not obtained during the critical 4 to 6 hours during which infarct size might have been modified

Use of the too little and too late dosage regime of these early trials is explainable by an exaggerated fear of left ventricular failure and collapse from beta blockers particularly if they are given intravenously Evidence for this was mainly anecdotal[16] or else reported in insufficient detail It was also to a large extent refuted by Mueller and colleagues[18] who showed that propranolol in a dose of 0 1 mg /Kg can be given safely intravenously to patients with uncomplicated full thickness infarcts who were studied within 24 hours of the onset of the infarct and had

hemodynamic monitoring in a coronary care unit[1] Subsequent experience has confirmed their results and beta blockers have indeed been used successfully in patients with established heart failure due to congestive cardiomyopathy[1]

Using Mueller and associates dosage regime we have measured total creatine kinase appearance and peak levels in a randomized trial of patients seen within 12 hours of onset of an uncomplicated infarct which appeared to be transmural on electrocardiographic criteria Although no objective clinical benefit could be demonstrated from propranolol in this group of uncomplicated patients there were no serious side effects from the drug and the enzyme levels were some 30% lower on average in patients who were treated within 4 hours of the onset than in control patients If treatment was delayed beyond 4 hours there was no significant difference between enzyme levels in the treated and control patients In a subsequent study of patients with a typical history of recent prolonged chest pain but no diagnostic ECG changes we were able to show that fewer completed infarcts occurred in treated patients than in controls[1] It thus appeared that threatened infarction in some cases could be prevented by early and adequate beta adrenoceptor blockade

If beta blockers given early and in adequate dosage can indeed restrict infarct size it is possible that a useful effect on early mortality may be seen only in patients with potentially large infarcts which could cause shock and cardiac failure However abolition of the inotropic adrenergic stimulus might make cardiac failure worse thus there is a potential dilemma in the use of beta blockade for the complicated patient seen early after the onset Could treatment be given safely and with benefit for such patients? Preliminary results from our own coronary care unit suggest that intravenous propranolol given cautiously with hemodynamic monitoring and in combination with intravenous furosemide does not exacerbate cardiac failure in patients who are already in mild failure after an infarct In a small group of such patients who had slight breathlessness radiologic evidence of interstitial pulmonary edema and a raised pulmonary wedge pressure the wedge pressure was not raised further by propranolol and clinical improvement [illegible] urred with clearing of the pulmonary edema [illegible] statistical significance can be attached to these [illegible] results but they do suggest that further clinical trials using hemodynamic monitoring are indicated for patients with early cardiac failure seen on admission to a coronary care unit

In addition to the above larger clinical trials are necessary using beta blockers given intravenously (if possible before admission to hospital) for patients with severe chest pain suggestive of infarction Administration of beta blockers intravenously outside hospital would appear to be a safe procedure, provided patients were admitted immediately to a coronary care unit and provided domiciliary treatment was avoided for patients with overt heart failure hypotension marked bradycardia or a history of asthma Parasympathetic over activity which is as common as sympathetic over activity in the very early stages after infarction[2] might be more pronounced after beta blockade However excessive parasympathetic activity is less likely to be dangerous than sympathetic over activity[1] and marked bradycardia can in any case be reversed by a small dose of atropine given intravenously Thus increased parasympathetic activity is not an absolute contraindication to beta blockade Large scale clinical trials of this nature will be necessary in order to determine whether restriction of infarct size by beta blocking drugs is of clinical benefit by reducing both short term and long term mortality after acute myocardial infarction

REFERENCES

1 Maroko P R Libby I Ginks W R Bloor C M Shell W E Sobel B F and Ross J Coronary artery reperfusion I Early effects on local myocardial function and the extent of myocardial necrosis J Clin Invest 31 2710 1972
2 Reimer K A Lowe J E Rasmussen M M and Jennings R B The wave front phenomenon of ischemic cell death 1 Myocardial infarct size versus duration of coronary occlusion in dogs Circulation 56 [illegible] 19[illegible]
3 Maroko P R, Kjekshus J K Sobel B E Watanabe T Covell J W Ross J and Braunwald E Factors influencing infarct size following experimental coronary artery occlusions Circulation 43 6[illegible] 1971
4 Reimer R A Rasmussen M M and Jennings R B Reduction by propranolol of myocardial necrosis following temporary coronary artery occlusion in dogs Circ Res 33 353 1973
5 Miura M Thomas R Ganz W, Sokol T Shell W E, Toshimitsu T, Kwan A C and Singh B N Effect of delay in propranolol administration on reduction of myocardial infarct size after experimental coronary occlusion in dogs Circulation 59 1148 1979
6 Raab W Adreno sympathogenic heart disease (neur[illegible]

humoral factors in pathogenesis and treatment) Ann Intern Med 28 1010 1948

Gazes P C., Richardson J A and Woods E F Plasma catecholamine concentration in myocardial infarction and angina pectoris Circulation 19 657 1959

Graham T P Covell, J W Sonnenblick, E H Ross J Jr and Braunwald E Control of myocardial oxygen consumption relative influence of contractile state and tension development J Clin Invest 47 375 1968

Alleyne G A C., Dickinson C J., Dornhorst A C., Fulton R M Green K C., Hill, I D Hurst P Laurence D R Pilkinton T Pritchard B N C., Robinson B and Rosenheim M L. Effects of pronethalol in angina pectoris, Br Med J 2 1226 1963

Balcon, R Jewitt D E Davies, J P H., and Oram S A controlled trial of propranolol in acute myocardial infarction Lancet 2 917 1966

Clausen J., Felsby M Jorgensen F Nielsen B D Roin, J and Strange B Absence of prophylactic effect of propranolol in myocardial infarction Lancet 2 920 1966

2 Multi centre Trial Propranolol in acute myocardial infarction Lancet 2 1453 1966

3 Norris, R M Caughey D E., and Scott, P J A trial of propranolol in acute myocardial infarction Br Med J 2 398 1968

4 Nies, A. S., and Shand D G Clinical pharmacology of propranolol, Circulation 52 6, 1975

5 Rutherford J D Singh, B N Ambler P K and Norris R. M Plasma propranolol concentration in patients with angina and acute myocardial infarction Clin. Exp Pharmacol. Physiol 3 ?37 1976

16 Ten years of propranolol A symposium on the history and the future of beta blockade Postgrad Med J 52(Suppl 4) 1976 p 152

17 Bay G Lund Larsen, P Lorentsen E., and Sivertssen E Haemodynamic effects of propranolol (inderal) in acute myocardial infarction Br Med J 1 141 1967

18 Mueller H., Ayres S M Religa A and Evans R G Propranolol in the treatment of acute myocardial infarction Effect on myocardial oxygenation and hemodynamics, Circulation 49 10 8 1974

19 Waagstein F Hjalmarson A Varnauskas E and Wallentin I Effect of chronic beta adrenergic receptor blockade in congestive cardiomyopathy Br Heart J 37 1022 19 5

20 Peter T Norris, R M Clarke E D Heng M K., Singh, B N., Williams, B., and Howell, D R Reduction of enzyme levels by propranolol after acute myocardial infarction, Circulation 57 1091 1978

21 Norris R M., Clarke E D., Sammel, N L., Smith, W M and Williams, B Protective effect of propranolol in threatened myocardial infarction, Lancet 2 907 1978

22 Pantridge J F Adgey A. A J Geddes J S., and Webb S W The acute coronary attack London 1975 Sir Isaac Pitman & Sons, Ltd p 28

23 Myers R W., Pearlman A. S., Hyman R M. Goldstein R. S Kent K M Goldstein R E and Epstein S E Beneficial effects of vagal stimulation and bradycardia during experimental acute myocardial ischemia Circulation 49 943 1974

IMPORTANT
INFORMATION FOR AUTHORS

Effective June 1 1980 all manuscripts for the AMERICAN HEART JOURNAL should be sent to

Dean T Mason M D
Section of Cardiovascular Medicine
University of California
School of Medicine
Davis California 95616

An analysis of electrocardiographic radiographic, and vectorcardiographic findings in patients with implanted cardiac pacemakers

T K Kaul*
P W Macfarlane
R M Thomson
W H Bain
Glasgow Scotland

Electrocardiography and lateral chest radiographs are normally used to locate the site of implanted electrodes of cardiac pacing systems [1] Faults in the latter can be detected by routine bipolar lead electrocardiography but malpositioning of the implanted electrodes is more difficult to determine The morphology of QRS complexes in a 12 lead ECG is a valuable but not an infallible guide to the site of stimulation [3] while interpretation of lateral chest radiographs also has limitations Vectorcardiograms have also been reported as being of use in the study of both the pacing system[5] and the intracardiac conduction system [6 7] but little attention seems to have been paid to the pacemaker artefact stimulus and to early ventricular depolarization vectors in the detection of electrode placement errors The present study was undertaken to determine whether the following three techniques would in combination provide a reliable indication of electrode placement errors and their site of implantation

1 Pacemaker artefact vectors as determined from the three orthogonal lead ECG (and hence the vectorcardiogram)

2 QRS morphology from three orthogonal lead and 12 lead ECGs and

3 Chest radiographs

From the University Departm nts of Cardia S ge y and Med cal Cardiology Royal Infirm ry Gla g w Scotla d

Received for publication June 12 1 79

Accepted for publication Oct 19

Reprint requests Mr W H Ba Dr Su g ry Royal Infirmary Gla g w C4 0SF S tl d

Present address Broadgreen Hospital L rp l

Patients and methods

Serial 12 lead ECGs and chest radiographs (lateral and posteroanterior views) of 300 consecutive patients were recorded and studied after the implantation of permanent pacemakers The nature of any preoperative conduction defect and site of myocardial infarction in relevant cases were also considered Two hundred and ninety seven patients received transvenous and three had epicardial systems The age range of patients in this group was 33 to 94 years while individual recordings were made at any time between 1 day and 8 years after the implantation Vectorcardiograms derived from the modified axial three orthogonal lead system were recorded in all patients who presented with abnormal x ray appearances or an abnormal ECG—i.e not type A or B (see below)—while a sample of patients with a normal 12 lead ECG and x rays also had vectorcardiograms analyzed

The 12 lead ECGs were classified into eight different groups as follows

Type A LBBB with LAD and tall R in Leads V_5 V_6

Type B LBBB with LAD and dominant S in Leads V_5 V

Type C LBBB with LAD $R > 0.2$ mV in Leads V_1 or V_2 or V_3

Type D IVCD with extreme LAD and dominant S in Leads V_1 V_6

Type E RBBB with RAD

Type F Probable bilateral bundle branch block with LAD

Type G RBBB with extreme left axis deviation

Type H Sinus rhythm

0002 8 03/80/060686 + 08$00 80/0 © 1980 The C V Mosby Co

Table I 12 lead ECG patterns and site of implantation of pacing electrodes in 300 patients (297 endocardial 3 epicardial)

Type	ECG patterns	Number of patients	Position of pacing electrode in lateral x ray				
			Epicardium	RV apex	RV body	RV outflow tract	Posterior
A	LBBB with LAD and tall R in V V	84	–	74	8	2	–
B	LBBB with LAD and dominant S in V V	145	–	117	17	5	6
C	LBBB with LAD and R < 0.2mV in V V or V	27	–	11	12	2	2
D	LVCD with RAD and dominant S in V V	1	–	–	–	–	1
E	RAD & RBBB	4	3	–	–	–	1
F	Probable bilateral bundle branch block with LAD	2	–	–	1	–	1
G	RBBB and extreme left axis deviation	3	–	–	–	–	3
H	Sinus rhythm	34	–	34	–	–	–
	Totals	300	3	236	38	9	14

Abbreviations RV = right ventricle LBBB = left bundle branch block RBBB = right bundle branch block LAD = left axis deviation RAD = right axis deviation.

The single channel electrocardiograph used to record the 12 lead ECG had a low frequency response (flat to under 50 Hz) The three lead ECGs were recorded with amplifiers having a response flat to 200 Hz and were written out on an Elema 34 ink jet writer with a superior response While each of these frequency responses is inadequate for exact measurement of pacemaker stimulus amplitude they are sufficient to determine the polarity of the stimulus in each lead An approximate direction of the stimulus vector can thus be inferred This vector was classified as being directed superiorly (S) or inferiorly (I) posteriorly (P) or anteriorly (A) and to the right (R) or left (L) The mean spread of ventricular excitation up to approximately 20 msec after QRS onset was also determined from the three lead ECG and was described in similar terms Vectorcardiographic loops were plotted on a PDP8E computer after analogue to digital conversion of the ECG signals A typical complex was selected for display

X rays were used to determine whether the pacing catheter was pointing anteriorly or otherwise—i e a line joining proximal to the distal electrode would point anteriorly in the lateral x ray of a normally implanted electrode catheter

Results

The 12 lead ECG patterns and radiological appearances of the implanted pacemakers in the 300 patients are summarized in Table I Two hundred twenty nine of these patients had a normal LBBB pattern (76 3%) type A was found in 84 (28%) and type B was found in 145 patients (48 3%) Abnormal type C LBBB (with LAD and a prominent R wave in Leads V_1 V_2 or V_3) was found in 27 patients (9%) In this group the catheter electrode pointed essentially retrosternally or towards the RV base in all but two patients in whom it was directed posteriorly (Table I) The other ECG patterns types D to G were found in only 10 patients

The catheter electrode system was directed retrosternally in 95% of patients although the catheter tip was in the RV body in 38 (12 7%) or in the outflow tract of the right ventricle in 9 patients (3%)

The normal pattern of the stimulus artefact was SPR in agreement with the findings of others[4] although a number of patients with a normal QRS morphology and x ray appearance had an SAR pattern of stimulus artefact together with IPL or SAL initial excitation patterns the important point being a leftward ventricular depolarization Some patients were difficult to

Table II Unusual ECG and x ray findings and the QRS vectors in 17 patients

Number of patients	Position of electrode in lateral x ray	ECG pattern	Pre-operative conduction defect	Pacing stimulus	Initial cardiac excitation	Site implantation
1	Posterior	B	Sick sinus	SAR P	SPL	RV
2	Posterior	B	MI CHB	SAR	IPL	RV
3	Posterior	B	CHB	SPR	SPL	RV
4	Posterior	B	CHB	SAR	SPL	RV
5	Posterior	B	CHB	SAR	SPL	RV
6	Posterior	C	CHB	SPR	IAL P	RV
	Posterior	C	Sick sinus	SPR	IPL	RV
8	Posterior	B	Sick sinus	SPR	SPI	RV
9	Posterior	D	2 1 AV block	SPL	SPR	Coronary venous system
10	Posterior	G	L post hemiblock MI	IAR	SPR	Coronary venous system
11	Posterior	G	CHB	IAR	SPR	Coronary venous system
12	Posterior	G	CHB	SPR	SPR	Coronary venous system
13	Posterior	E	CHB	SPR	SPR	Coronary venous system
14	Posterior	F	2 1 RBBB MI	SPL	SAR L	Coronary venous system
15	Anterior	C	CHB	SPL	SPR	Perforation RV
16	Anterior	C	CHB	IPR	IPR	Perforation RV
17	Anterior	C	CHB	IPR	SPR	Perforation RV

RV = right ventricle MI = myocardial infarction CHB = complete heart block AV = atrioventricular
Key to ECG patterns as in Table I Key to pacing stimulus and Cardiac Excitation as described in text

type in that the stimulus artefact was generally large and biphasic In cases of doubt the initial component of the stimulus was chosen as indicative of the stimulus direction

The normal pattern of early ventricular depolarization with RV stimulation was mainly SPL This is in agreement with the findings of Zonerach and colleagues but at slight variance with the findings of Castellanos and co workers who referred to the initial delay of the stimulus artefact rather than to early ventricular depolarization In their series of patients with transvenous pacing it would appear that 80% had biphasic stimulus artefact which was not the case in our series

In all but 17 patients the ECG x ray and stimulus vector agreed on the normal or abnormal position of the pacemaker electrodes The details of these 17 patients are presented in Table II In 14 patients (4 7 %) the pacing electrode system was directed posteriorly and the ECG pattern was either B C D E F or G The initial propagation of excitation in these 14 patients is outlined in Table II which also summarizes the stimulus artefact vectors This table also includes three other patients with an unusual combination of ECG VCG and x ray findings Each of them had a perforated right ventricle

Discussion

Although the pattern of normal LBBB occurred in 229 patients (76 3%) the catheter electrode was anterior in 233 and posterior in six, the latter group all having type B pattern Stimulation of the basal portion of the right ventricle will generate an LBBB pattern with base to apex excitation while the electrical axis will point to the left and inferiorly either on account of (a) an endocardial electrode falling short of the apical position in RV or (b) an electrode bent against the septum or (c) epicardial leads implanted at the base of the RV Since the electrode system normally lies in an anterior position—i.e., a line from the proximal to the distal electrode points anteriorly the 223 out of 229 patients with type A or B ECG were regarded as having the pacing system in the RV apex The six out of 229 patients with a posteriorly directed catheter system were considered as possibly having the electrodes in the coronary venous system • This point will be discussed below

In the 27 patients with type C ECG the pacing electrode system was directed anteriorly in 25 and posteriorly in two The initial QRS activation was directed to the left posteriorly and superiorly in all but three of 27 patients in whom the initial QRS vector was directed to the right posteriorly

and superiorly (Fig 1) These three patients also presented with exit block and an early penetration of myocardium occurred as indicated by intermittent diaphragmatic twitching (patient No 15 Table II) presence of sanguinous effusion and clots within the pericardium (patients No 16 and 17 Table II) and resistance encountered when the catheter electrodes were dislodged at the implantation of a new epicardial electrode system

It might be postulated that the variation in the QRS pattern in the precordial leads in Types A B and C is due to differing relationships of the left and right ventricles and the anteriorly placed stimulating electrode

Despite the widespread use of pervenous RV pacing occurrence of an RBBB pattern during RV pacing is an infrequent finding The explanations suggested for this finding are (a) perforation or an early penetration of RV (b) retrograde conduction of the excitation wave through the conduction system of the heart* (c) spread of impulses across the Purkinje bridge between the left and right sided conducting systems at the apex (d) high position of the electrode stimulating the mid septum which is usually thin and may therefore depolarize the LV first or (e) RV activation delay due to disease of the conducting system of the right ventricle According to Sodi Pallares and Calder's[11] concept of septal anatomy similar QRS patterns can be obtained after the stimulation of the apex of the heart at either side of the interventricular septum

The electrical stimulation of left ventricle (by an epicardial lead or an endocardial electrode misplaced into the coronary venous system [Fig 2] or by an endocardial electrode which has perforated the myocardium) provides a classical RBBB pattern[10] However the QRS complexes and pattern of excitation may vary with the exact site of LV stimulated The electrical axis is orientated to the right and inferior by with superior implantation If the electrode is adjacent to the apex and situated (though not orientated) anteriorly the general excitation will occur to the right posteriorly and superiorly due to the spread of excitation in the RV being dominant producing S waves from Leads V to V in the ECG (Case 9 Table II)

A more anterior position will yield an initial R wave in both Leads V and V while a slight posterior deviation produces a negative deflection in Lead V_2 but still with an R wave in Lead V

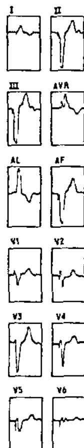


Fig 1 The initial ventricular excitation is to the right posteriorly and superiorly in a patient with type C ECG pattern the catheter electrode was directed to the anterior

With the stimulation of the posterobasal portion of LV the activation may proceed through the septum as well as laterally and superiorly This produces LAD and the net effect in the transverse plane is a resultant anteriorly directed QRS vector giving a tall R wave in Lead V_2 with diminishing R waves on either side—i e to Leads V and V_6 respectively

A bipolar pacing system is an ideal model of an electrical dipole with a source and sink for electrical current which should flow directly from one electrode to the other during activation of the system Thus if the direction of the stimulus current is measured using an orthogonal lead system the approximate orientation of the electrode system can be determined electrocardiographically For example in the normal situation an electrode system will lie in the apex of the RV pointing anteriorly with the proximal electrode superiorly positioned with respect to the distal electrode The stimulus vector will then be orientated along a line from the distal to the

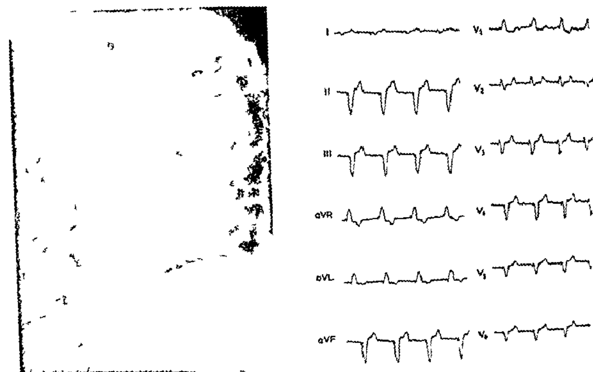


Fig 2 Lateral chest x ray the electrode system is orientated posteriorly The ECG shows LAD RBBB (Type G)

proximal electrode and normally will therefore be directed superiorly posteriorly and generally to the right side of the patient—i e at about 10 o clock as seen from the front above and also as seen from the right (i e right sagittal view) A normal stimulus v[illegible] therefore described as SPR If the el[illegible] system is directed posteriorly (Fig 2) an [illegible] directed stimulus vector would be expected This was not always found and it is suspected that at the time of operation the connection to the generator was reversed to produce an expected negative deflection of the stimulus artefact in Leads I II and III

With respect to early ventricular depolarization the pattern noted in the normal was SPL With RV apical stimulation it appeared that in the typical normal the resultant ventricular depolarization was directed superiorly to the left presumably being due to the net effect of septal and LV free wall excitation in an apex base direction

The posterior position of transvenous endocardial electrodes in a lateral chest x ray as found in 14 patients (Table II) has been considered diagnostic of malpositioned electrodes in the coronary venous system [1] However interpretation of the lateral chest x ray alone can be misleading In eight patients in the present series although the catheter electrode was directed posteriorly (Table II) the 12 lead ECG patterns (B or C) together with the stimulus (SAR or SPR) and excitation (SPL or IPL) vectors suggest that the pacing electrode was in the RV (Fig 3 A and B) In the remaining six patients x ray ECG and vector findings were unequivocally suggestive of malpositioning of the electrode in the coronary venous system (ECG pattern D E F G and initial excitation SPR) (Table II) In all but three patients with malpositioned electrodes (patients No 7 8 and 14 Table II) intermittent failure of pacing occurred and resiting of the electrodes was necessary After minimal displacement it was possible to advance the malpositioned electrode in the right ventricle into the main pulmonary artery at remanipulation The malpositioned electrodes in the coronary sinus had to be passed through the tricuspid valve at the reimplantation At each subsequent repositioning a satisfactory implantation of the electrodes into the right ventricular apex was confirmed with the help of a lateral chest x ray and vectorcardiogram

An overzealous attempt to implant the catheter electrode into the RV apex in the frontal projection may result in bending of the catheter electrode tip against the septum or the floor of the RV With such a malpositioned RV electrode



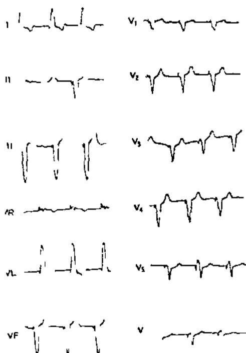


Fig 3A Lateral x ray the electrode system is orientated posteriorly The ECG shows LAD and LBBB (Type B)

the pacing may be intermittent due to the instability of the electrodes and in a lateral x ray it could point posteriorly but the excitation pattern as determined with the ECG and vectorcardiogram would indicate RV stimulation Thus although such a malpositioned electrode in the RV may present identical to an electrode placed into the coronary venous system clinically and radiologically it can be correctly diagnosed by studying the excitation pattern with 12 lead ECG and vectorcardiogram The findings can be summarized as in Fig 4 where a diagnostic tree is presented From this it can be seen that the VCG findings are of value in a limited number of patients If a strict procedure for connection of the pacemaker electrode were to be followed the posterior or anterior orientation of the electrode catheter with the help of pacemaker stimulus artefact could be inferred even in the absence of a lateral chest radiograph

Conclusions

The interpretation of the morphology of the 12 lead ECG and appearances of the lateral chest radiographs are valuable but not an infallible guide to the site of implantation of the pacemaker electrodes A simple analysis of stimulus artefact



Fig 3B QRS vector of the same patient as in *Fig 3A* Initial ventricular excitation is to the left, posteriorly and superiorly

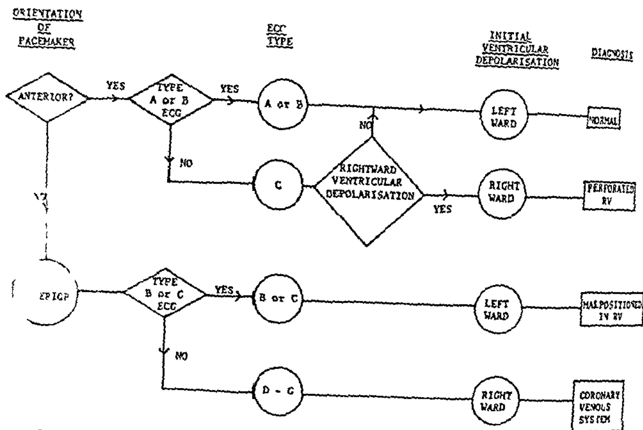


Fig 4 A diagnostic tre … for … ating the pacemaker electrodes A *diamond* encloses a question while a *circle* encloses a descriptive … t

and initial ventric a … n vectors in combination with l … and lateral chest radiograph. ha … ful in diagnosing the electrode mal … rrors in the post implantation per … t the time of implantation

Summary

In patients with implanted cardiac pacemakers, the radiological appearances and the configuration of the 12 lead ECG have been conventionally used both to locate the site of the electrode implantation and to diagnose electrode placement errors These techniques have limitations and in the present study vectorcardiographic data derived from the pacemaker stimulus and the spread of ventricular depolarization has been added to improve accuracy Three hundred patients with implanted cardiac pacemakers were studied Unusual QRS complexes as determined from the 12 lead ECG were found in 37 (12%) and the position of the pacemaker electrodes determined from the lateral chest x ray was outside normal (R V apex) in 61 patients (20.3%) A combined interpretation of the ECG chest x ray and the vectorcardiogram agreed on positioning (correct or incorrect) in all but 17 patients (5 6%). Three patients had a perforated right ventricle while further study of the other 14 suggested malpositioning of the catheter electrode in the right ventricle or in the coronary venous system. An analysis of the ECG patterns x ray appearances and vectorcardiograms is presented with respect to the diagnosis of pacemaker electrode placement errors and a logical tree for establishing the position of the pacemaker is introduced

The authors are grateful to Mr F M Towler and Miss Jean McDonald of the Medical Illustration and Photography Section of the University Department of Surgery Royal Infirmary Glasgow and to Miss P Robinson for their help in the preparation of the manuscript

REFERENCES

1 Meyer J A., and Miller K Malplacement of pacemaker catheters in coronary sinus J Thorac Cardiovasc Surg 57 511 1969
2 Thomas D L and Green D G Improvements in the technique of assessing implanted cardiac pacemakers Med Biol Engineering 12 589 1974
3 Castellanos A Unusual QRS complexes produced by pacemaker stimuli Am Heart J 77 432, 1969
4 Kaul, T K., and Bain W H Radiological appearance

of implanted transvenous endocardial pacing electrodes Chest 72 323 1977
5 Macfarlane P W, and Green G D Vectorcardiographic studies of implanted cardiac pacemaker stimuli, Annals of the Medical Section of the Polish Academy of Sciences 16 345 1971
6 Castellanos A, Lemberg L Salhanick L, and Berkovits, B Pacemaker vectorcardiography AM HEART J 75 6 1968
7 Zoneraich O Zoneraich E and Douglas, A H The vectorcardiographic findings in patients with artificial pacemakers, Dis. Chest 53 436 1968
8 Macfarlane P W A modified axial lead system for orthogonal lead electrocardiography Cardiovasc Res 3 510 1969
9 Mower M M, Arange O E and Tobatznik, B Unusual patterns of conduction produced by pacemaker stimuli AM HEART J 74 24 1967
10 Barold S S, Narula O S Javier R P, Linhart J W, Lister J W, and Samet P Significance of right bundle branch block patterns during pervenous ventricular pacing Br Heart J 31 285 1969
11 Sodi Pallares D and Calder R M New bases of electrocardiography London 1956 H Kimpton
12 Ragaza E P, and Shapiro R Radiological recognition of unusual sites of a transvenous catheter pacemaker J Can Assoc Radiol 21 214 1970

Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978 Therefore all manuscripts must be accompanied by the following written statement signed by one author The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C V Mosby Company in the event the work is published The undersigned author warrants that the article is original is not under consideration by another journal and has not been previously published I sign for and accept responsibility for releasing this material on behalf of any and all co authors Authors will be consulted when possible regarding republication of their material

Large multiple coronary artery aneurysm in adult patients a report on three patients and a review of the literature

B Letac M D F A C C
J L Cazor M D
A Cribier M D
C Sibille M D
C Toussaint M D
Fran

Aneurysms of the coronary arteries are uncommon In 1929 Packard and Wechsler[1] found only 31 published cases in addition to that which they were reporting In 1963 before the development of coronary angiography Daoud and associates[2] published 10 personal cases and collected another 89 cases from the literature

In spite of the widespread use of coronary angiography coronary ... aneurysms remain an uncommon ... since 1963 fewer than 150 new ... published in the literature ... logy of these aneurysms ... nine Most coronary ... out in patients with ... and aneurysms discovered ... ns are readily attributed to the ... the other main etiological explanation being that ... are congenital The appearance and circumstances of the aneurysms are the main factors pointing to their etiology In some cases however the appearance of the coronary aneurysms is so peculiar that they cannot immediately be attributed with certainty to one or other of the main causes congenital or atherosclerotic This was the case in the three patients reported here They were selected from about 2 000 coronary angiographies among which there were moreover ten cases with small isolated aneurysms of the coronary arteries which were the seat of advanced atherosclerosis and one case with an aneurysm of bacterial origin published previously[3]

From Service des Soins Intensifs Cardiologiques et des Explorations Hémodynamiques Cardio Vasculaires, Centre Hospitalier et Universitaire Hôpital Ch les Nicolle Rouen France

Received for publication Sept 6 1979
Accepted for publication Dec 11 1979

Reprint requests B Letac Service des Soins Intensifs Cardiologiques et des Explorations Hémodynamiques Cardio Vasculaires, Centre Hospitalier et Universitaire Hôpital Charles-Nicolle ... 76000 Rouen, France

*This survey is incomplete ... no mention is made of the two cases published by Batzenschlag et al.

Case reports

Patient No 1 S A 45 years old male The patient was admitted to the hospital on June ... 1974 with an anteroseptal myocardial infarction. There was no history of any particular illness in childhood beyond the usual ones the patient being unable to give further details There was no previous history of angina apart from some constrictive chest pains during the days before the infarction Certain coronary risk factors were present moderate cigarette smoking blood cholesterol of 2 95 g /L and mild diabetes

In view of his relatively young age hemodynamic and angiographic investigations were performed 2 months after the acute attack These showed a large anteroapical aneurysm of the left ventricle considerably altering the ventricular function with an end diastolic pressure of 29 mm Hg On coronary angiography the appearance of the coronary arteries was most unusual in that both arteries were the seat of multiple large aneurysms (Fig 1A) The right coronary artery was distorted throughout its course by a number

0002 8 03/80/060691 + 07$00 70/0 © 1980 The C V Mosby Co

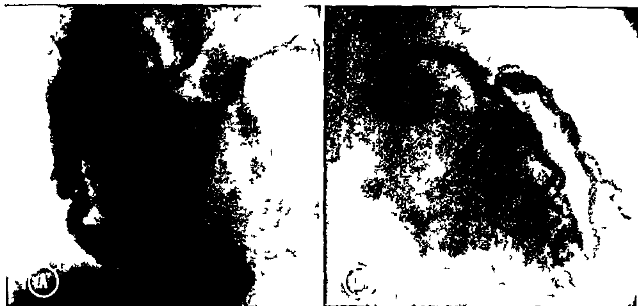


Fig 1 Case No 1 *A* right coronary artery in the left anterior oblique projection *B* Left coronary artery in the right anterior oblique projection

of large aneurysms of about 1 5 cm in diameter and several centimeters in length and the aneurysmal areas were separated by short segments of constriction the degree of which was difficult to evaluate The distortions were such that the appearance in the left anterior oblique position was reminiscent of the colon outlined by barium There was also a considerable dilatation with at least two aneurysmal sacs of which one was nearly 2 cm in diameter of what is seemingly a conus artery but could possibly be a circumflex artery arising from the right coronary The left coronary artery (Fig 1*B*) was also the seat of a number of aneurysms mainly on the left anterior descending artery and on the diagonal branch with an aneurysmal sac of more than 2 cm in diameter at the origin of this vessel

There was no possibility of surgery on such a coronary tree, and the patient was treated with oral anticoagulants (acenocoumarin) clofibrate and digoxin Three years later his condition was satisfactory without evidence of cardiac failure or thoracic pain

Patient No 2 P B 43 years old male The patient was admitted to the hospital on June 6 1977 with a posterior myocardial infarction without previous chest pain apart from angina with spontaneous pains which disappeared after a few days without any special treatment when he was aged 38 The course of the infarction was satisfactory In his previous history there was a tonsillectomy at the age of 36 for frequent sore throats but this patient had no history of any particular illnesses in childhood other than the common ones no further details were obtained As regards the coronary risk factors there was only a moderately raised blood cholesterol (2 80 g /L) and a little overweight

In view of his relatively young age hemodynamic and angiographic investigations were performed 4 months after the infarction The left ventricle was slightly dilated with moderate impairment of contractility The end diastolic pressure was 18 mm Hg The appearance of the coronary system was quite unusual because of the presence of several large aneurysms The main trunk of the left coronary artery the origin of the left anterior descending artery and the circumflex artery were considerably but irregularly dilated attaining over all a caliber of more than 1 cm (Fig 2*A*) The first part of the circumflex artery in particular showed a fusiform dilatation which reached 1 5 cm in diameter before the vessel divided into two branches one of which was the site of two other fusiform aneurysms of 0 8 to 0 9 cm in diameter No significant over all narrowing was seen in the left coronary tree The right coronary artery (Fig 2 *B*) was also the site of large aneurysms 2 to 3 cm in length especially on the right border of the heart with a diameter





Fig 2 Case No 2 *A* Left coronary artery in the right anterior oblique projection *B* Right coronary artery in the left anterior oblique projection

reaching 10 to 12 mm Between the two aneurysms and beyond the second there was an area of narrowing which seemed to reduce the lumen of the artery considerably

After 18 months follow up the patient had no chest pain and his activities were normal His only treatment has been with oral anticoagulants (acenocoumarin)

Patient No 3 J M R 31 years old male The patient was admitted to the hospital on November 21 1978 for coronary angiography on account of angina pectoris The first attack of angina was in February 1978 with pain lasting for 3 hours without definite E C G changes but with a moderate rise in CPK enzymes Since then he had had angina of effort and an exercise tolerance test in July 1978 was positive There was a report of high blood cholesterol (4 40 g /L) in 1975 and when seen following treatment with clofibrate it was 3 25 g L and the triglycerides were 0 70 g /L There was a family history of hypercholesterolemia which was also present in his mother and two sisters There was no other special previous medical history except for the usual childhood illnesses Clinical examination was normal as was the chest x ray

During hemodynamic [illegible] n the pressures were normal and the [illegible] dex was 2 66 L /min /M² Ventricul [illegible] d moderately poor contractility with an ejection fraction of 48% During opacification of the coronary arteries the observer was at first struck by the very peculiar appearance of the coronary network which was the seat of large aneurysms in the three main arteries There was an aneurysm 3 cm. in length and 2 cm in diameter occupying the first part of the left anterior descending artery but beyond this the artery appeared normal (Fig 3 *A*) In the right coronary artery (Fig 3 *B*) there were several large successive aneurysms separated by segments of artery of normal caliber and the posterior interventricular and left retroventricular arteries appeared normal No aneurysmal lesions on the collateral branches of the aorta were apparent on thoraco abdominal aortography

The question of a saphenous bypass graft on the left anterior descending and right coronary arteries beyond the aneurysm was discussed but as the patient was asymptomatic this was finally rejected and the patient was treated with oral anticoagulants (acenocoumarin) and clofibrate

Comments

Coronary aneurysms can vary in the number of lesions single or multiple and all shapes and sizes can be found They can vary from a small solitary aneurysm a few millimeters in diameter on a normal coronary tree or on altered coronary



Fig 3 Case No 3 *A* Left coronary artery in the left transverse projection *B* Right coronary artery in the left anterior oblique projection

arteries up to very large multiple aneurysms involving several branches of the coronary system The aneurysms may be saccular or fusiform in appearance The caliber of fusiform aneurysms may or may not be very large in which case unless they are separated by sections of artery with a normal or restricted caliber their boundaries can be difficult to determine with diffuse dilatation of the arteries which have been termed megadolichoid coronary arteries[5] or coronary ectasia

In the survey of the subject by Daoud and associates in 1963 all the ten personal cases reported were considered atherosclerotic There was only one case of multiple aneurysms involving both coronary arteries and there were only 11 such cases among the 89 collected by the authors from the literature Since Daoud s review a total of 140 cases have been described in the English and French literature generally seen during life by means of coronary angiography The number of cases discovered in relation to the total number of coronary angiograms performed was 92 in 9 105 investigations

Four main causes of coronary aneurysms can be recognized from their clinical context and the appearance of the lesions Congenital aneurysms are generally large and situated on one coronary artery generally the right coronary and are most commonly found in young subjects Atherosclerotic aneurysms are usually small in size and either localized or consisting of dilatations variable in extent with a relatively small diameter equal to or under 1 cm associated with stenotic lesions of the usual atherosclerotic type in the remainder of the coronary risk factors On the whole they are very uncommon in relation to the high frequency of atherosclerotic coronary artery disease Aneurysms of bacterial origin are exceptional They are small solitary and can only be recognized when there is a clear history of septicemia and when the remainder of the coronary system is normal Finally coronary aneurysms may have an inflammatory basis but this category is usually seen in small children in association with two principal conditions periarteritis nodosa and a special condition which was first described in Japan—the mucocutaneous lymph node syndrome This condition which was initially described by Kawasaki and associates in Japanese in 1967 and in English in 1974[6] seems to be especially common in Japan where it was first described Up to 1977 more than 10 000 cases had been reported in that country[7] The syndrome is characterized by fever exanthema enanthema and adenopathy, and is most prevalent in male children under the age of 5 subsiding after about a fortnight Death occurs in 1% or 2% of cases from myocardial infarction due to thrombosis of an inflamed artery or coronary aneurysm In a

study of 20 cases in children aged 4 to 8 coronary angiography was performed some weeks or months after the illness Coronary aneurysms five of which were multiple were found in seven cases (35%) and nonaneurysmal abnormalities were discovered in another five cases[8] A later study showed the same proportion of coronary aneurysms[9] This recently described illness is thus associated in more than a third of cases with coronary lesions distinguished by the number and size of the aneurysms which involve the whole coronary tree and which may sometimes regress However although this condition was first described in Japan and seems to be unduly frequent in that country it has also been reported in other countries for example in the United States Canada Greece Great Britain and France[3, 7, 10, 1] It is not therefore a specifically Japanese illness With this syndrome could be considered periarteritis nodosa[2] and other panangitis which in children may frequently cause coronary aneurysms of the same type i e large and multiple and involving several coronary arteries[3] the histology of which is very similar to that of the mucocutaneous lymph node syndrome[6] and which is also capable of regressing

Most coronary aneurysms in the literature except in the Japanese publications have been thought to be either congenital or atherosclerotic In the patients described by Dawson and Ellison by Ghahramani and associates[6] by Kaufmann and colleagues[7] by Mattern and collaborators by Seabra Gomes and associates[9] by Wilson and co workers[30] as well as in 15 of the 89 cases analyzed by Daoud and associates[2] a congenital origin was proposed In fact although this etiology may be the most probable in a large number of these cases quite often there is no supporting proof Atherosclerosis is more usually proposed as the etiological factor This was true in Daoud and colleagues 10 patients and in 47 of the 89 patients reported by them as well as in those recorded by Anabtawi and de Leon[31] by Batzenschlager and colleagues by Befeler and co workers[3] by Berkoff and Rowe by Bertelsen and Lindahl[3] by Cherner and collaborators[3] by Falsetti and Carroll by Gay and colleagues[36] by Halke and Edwards by Markis and associates[8] by Swanton and co workers and by Wilson and colleagues[4] Most of these aneurysms were probably really atherosclerotic mainly because most of them were seen in patients over 50 years of age they were not very large and they were associated with obviously atherosclerotic lesions in the remainder of the coronary system In some patients however the atherosclerotic etiology was not obvious especially in those seen in patients aged 40 or below

The other causes of aneurysm are much less common and those of bacterial origin are exceptional[3, 41] Apart from the special situation of the mucocutaneous lymph node syndrome only a few isolated coronary aneurysms of inflammatory origin have been published In the report by Roberts and Fetterman[4] the coronary arteries were involved in 18 out of 20 cases of childhood periarteritis nodosa 11 of whom had coronary aneurysms Other cases of coronary aneurysms associated with childhood periarteritis nodosa have been reported by Bertelsen and Lindahl,[4] by Glanz and co workers[4] and by Tang and Segal[3] Periarteritis nodosa is uncommon in childhood but the coronary arteries are frequently affected in this disease although this is exceptional in adults in whom the disease is more frequent In addition isolated cases of coronary aneurysm in children have been reported by Bocquet and associates[3] and by Dailly and co-workers[44] under the heading of diffuse arteritis of undetermined etiology In retrospect the latter case could have been due to the mucocutaneous lymph node syndrome a condition which was unknown at that time Lastly considering those of inflammatory origin there is one case published of multiple coronary aneurysms in an adult suffering from scleroderma[45] In addition to these etiological factors which on the whole occur in conditions which are fairly characteristic there are a number of cases in which the etiology remains completely unknown and the authors refrain from ascribing any cause to the aneurysms[3] This includes a recent series of 4? cases where the term ectasia rather than aneurysm was used as the lesions were characterized by diffuse dilatations[0]

In the publications on this subject during the past 10 years the part played by the mucocutaneous lymph node syndrome described by Japanese authors requires emphasis The etiology of this syndrome remains unknown but it appears to be a disease which has a very high incidence of coronary aneurysms An extensive experience of this unusual condition led Kitamura and associates[7] to suggest that before a coronary aneurysm is labelled atherosclerotic or congenital one

should consider the possibility of this syndrome occurring in childhood and passing unnoticed[7] On rereading the cases recorded in the literature it is noticeable that in many of these cases there are no precise facts or even any discussions on whether the aneurysms might be congenital or atherosclerotic in origin

In the three cases reported here the coronary lesions were probably not congenital and the aneurysms by their appearance size and the fact that they involved both coronary arteries can be clearly distinguished from those recorded in most of the publications on coronary aneurysms which were considered often on flimsy evidence as atherosclerotic or congenital in origin Bearing in mind the frequency of atherosclerotic coronary heart disease and the fairly standard characteristics of the lesions in this disease it is difficult to imagine how the aneurysms seen in these three patients could have been atherosclerotic Angiographically the lesions were highly exceptional in the size multiplicity and distribution of the aneurysms which chiefly affected the first parts of the main coronary arteries and did not show any of the usual features of coronary atherosclerosis even on the segments of arteries which were free from aneurysms—i e the irregular stenotic lesions which are characteristic of atherosclerosis One is also struck by the fact that these three cases concerned relatively young (42 and 45 years old) or definitely young (31 years old) men among the French population for atherosclerotic coronary artery disease and that no special risk factors were present in the first two cases In the third case there was an established familial hypercholesterolemia with a blood cholesterol of 4 30 g /L and some small tendinous xanthomas but even so it does not seem that one can incriminate atherosclerosis as the cause of the extensive aneurysmal lesions found in the coronary network. In fact no aneurysmal lesions have been described in familial hypercholesterolemia even in the severe forms where coronary lesions are very common but of the same type as those seen in atherosclerosis in general

In the three cases reported here it therefore seems justifiable to postulate that the lesions might have a different origin perhaps the sequel of a mucocutaneous lymph node syndrome or a regressive childhood periarteritis nodosa The angiographic appearances of the lesions are similar to those described in the mucocutaneous lymph node syndrome and the fact that no previous history suggestive of these two conditions is available in these patients is insufficient to exclude this possibility

Summary

Three cases of large multiple coronary aneurysms situated on both right and left coronary arteries were seen in three middle aged adult patients These patients were hospitalized for myocardial infarction in two cases and for angina pectoris in the third case On the coronary angiogram the coronary lesions were quite unusual as there were multiple voluminous aneurysms on both coronary arteries without evidence of atherosclerotic lesions of the remainder of the coronary tree These lesions did not seem to be congenital or atherosclerotic and it was postulated that these lesions might have been the sequelae of a mucocutaneous lymph node syndrome although no previous history of this condition could be found in these three patients

The authors wish to thank Dr M A Rugg Gunn for his assistance in the translation of this manuscript

REFERENCES

1 Packard M and Wechsler H F Aneurysm of the coronary arteries Arch. Intern Med. 43 1 1929
2 Daoud, A. S Pankin, D Tulgan, H., and Florentin, R. A Aneurysms of the coronary artery Report of ten cases and review of the literature Am J Cardiol. 11 228, 1963
3 Toussaint C., Letac B and Soyer R Anevrysme arteriel coronaire révelé par un infarctus myocardique compliqué d un anevrysme ventriculaire, Arch Mal. Coeur 1 97 1976
4 Batzenschlager A Le Gal Y and Hauswald R Les anevrysmes des arteres coronaires du coeur Arch. Mal Coeur 54 435 1961
5 Cherner F Neimann, J L., Cuilbere M., and Courtois sier A Anévrysmes atheromateux et mégadolichoarteres coronaires chez l adulte Coeur Med Interne 4 5_5 1976
6 Kawasaki, T Kosaki, F Okawa S Shigematsu I and Yanagawa, H A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan Pediatrics 54 271 1974
7 Kitamura S Kawashima Y., Kawachi K., Fujino M., Kozuka T Fujita T., and Manabe H Left ventricular function in patients with coronary arteritis due to acute febrile mucocutaneous lymph node syndrome or related diseases, Am J Cardiol 40 156 1977
8 Kato H Koike S Yamamoto M Ito Y., and Yano E Coronary aneurysms in infants and young children with acute febrile mucocutaneous lymph node syndrome J Pediatr 86 892, 1975
9 Onouchi, Z., Tomizawa N Goto M Nakata K., Fukuda M and Goto M Cardiac involvement and prognosis in acute mucocutaneous lymph node syndrome Chest 68 297 1975
10 Brown, J S Billmeier G J., Jr., Cox F., Ibrahim, M., Stepp W P., Jr., and Gibson R. Mucocutaneous lymph

node syndrome in the continental United States J Pediatr 88 81 1976
11 Casenave C and Aufrere A M Un cas de syndrome adeno-cutaneo muqueux Arch Fr Pediatr 35 555 1978
12 Goldsmith R W Gribetz D and Strauss L Mucocutaneous lymph node syndrome in the continental United States Pediatrics 57 431 1976
13 Gorin R Sorin M Meyer A Batisse A Toumieux M C and Mozziconacci T Le syndrome cutanéo muqueux et ganglionnaire de Kawasaki A propos d une observation compliquée d anévrysmes multiples Sem Hop Paris 54 442 1979
14 John T J de Benedetti C D and Zee M L Mucocutaneous lymph node syndrome in Arizona Am J Dis Child 130 613 1976
15 Lauer B A Bruhn F W Todd J K and Warren A Mucocutaneous lymph node syndrome in Denver Am J Dis Child 130 610 1976
16 Lyen K R and Brook C G D Mucocutaneous lymph node syndrome in two siblings Br Med J 1 1187 1978
17 Melish M E Hicks P M and Larson E Mucocutaneous lymph node syndrome in the United States Am J Dis Child 130 599 1976
18 Radford D J Sondheimer H M Williams G J and Rodney S Mucocutaneous lymph node syndrome with coronary artery aneurysm Am J Dis Child 130 596 1976
19 Rolland J C Lebranchu Y Nivet H Drucker J Chantepie A and Grenier B Syndrome de Kawasaki d évolution mortelle Nouv Presse Med 8 48 1979
20 Russel A S Zaragoza A J and Shea R Mucocutaneous lymph node in Canada Can Med Assoc J 112 1210 1975
21 Valaes T Mucocutaneous lymph node syndrome (MLNS) in Athens Greece Pediatrics 55 295 1975
22 Landing B H and Larson E J Are infantile periarteritis nodosa with coronary artery involvement and fatal mucocutaneous lymph node syndrome the same? Comparison of 20 patients from North America with patients from Hawaii and Japan Pediatrics 59 651 1977
23 Tang P H L and Segal A J Polyarteritis nodosa of infancy Fatal late complication J A M A 217 1666 1971
24 Clanz S Bittner S J Berman M A Dolan T F and Talner N S Regression of coronary artery aneurysms in infantile polyarteritis nodosa N Engl J Med 294 939 1976
25 Daw on J E and Ellison R G Isolated aneurysms of the anterior descending coronary artery Surgical treatment Am J Cardiol 29 868 1972
26 Ghahramani A Iyengar R Cunha D Jude J and Sommer L Myocardial infarction due to congenital coronary artery aneurysm (with successful saphenous vein bypass graft) Am J Cardiol 29 863 1972
27 Kaufmann H Dubost Ch Guilmet D Cachera J P Ecoiffier J and Leduc G Anévrysme solitaire de l artére coronaire droite traite avec succés par résection et greffe saphéne Arch Mal Coeur 8 1154 1970
28 Mattern A L Baker W P M H [illegible] J J and Lee D F Congenital coronary aneury m with angina pectoris and myocardial infarction tre [illegible] ith saphenous vein bypass graft Am J Cardiol 30 [illegible]
29 Seabra Gomes R Somerville J R [illegible] D N Emanuel R Parker D J and W ng M [illegible] coronary artery aneurysm Br Heart J 36 [illegible]
30 Wilson C S Weaver W F [illegible] d Forker A D Bilateral nonfistulous congenital coronary arterial aneurysms Am J Cardiol 35 319 1975
31 Anabtawi I N and de Leon J A Arteriosclerotic aneurysms of the coronary arteries J Thorac Cardiovasc Surg 68 226 1974
32 Befeler B Aranda J M Wells D E Machado H, El Sherif N and Lazzara R Coronary artery aneurysms in a population with ischemic heart disease Circulation 51 and 52 (Suppl II) II 158 1975
33 Berkoff H A and Rowe G G Atherosclerotic ulcerative disease and associated aneurysms of the coronary arteries AM HEART J 90 153 1975
34 Bertelsen S and Lindahl A Aneurysms of the coronary arteries Report of two cases Acta Med Scand 175 589 1964
35 Falsetti H L and Carroll R J Coronary artery aneurysm Circulation 51 and 52 (Suppl. II) II 1[illegible] 1975
36 Gay J Benoit P Tcherdakoff Ph Blondeau, Ph, Maurice P Bensaid J and Gerbaux E. Anévrysmes diffus des artéres coronaires Arch Mal Coeur 11 12[illegible] 1974
37 Kalke B and Edwards J E Localized aneurysms of the coronary arteries Angiology 19 460 1968
38 Markis J E Joffe C D Cohn P F Feen D J Herman M V and Gorlin R Clinical significance of coronary arterial ectasia Am J Cardiol. 37 217 1976
39 Swanton R H Lea T M Coltart D J Jenkins, B S Webb Peploe M M and Williams B T Coronary artery ectasia a variant of occlusive coronary arteriosclerosis Br Heart J 40 393 1978
40 Wilson C S Weaver W F and Forker A D Bilateral arteriosclerotic coronary arterial aneurysms successfully treated with saphenous vein bypass grafting Am J Cardiol 35 315 1975
41 Crook B R M Raftery E B and Oram S Mycotic aneurysms of coronary arteries Br Heart J 35 10[illegible] 1973
42 Roberts F B and Fetterman G H Polyarteritis nodosa in infancy J Pediatr 63 519 1963
43 Bocquet L Durup de Baleine D Bach Ch and Seringe Ph Ectasie des coronaires avec polyendarterite diffuse chez un nourrisson Ann Pediatr (Sem Hop Paris 40 84 1964
44 Dailly R Laumonier R de Menibus C H and Petit Bonveau G La coronarite aigue nécrotico thrombo ectasiante du nourrisson Presse Med 52 2006 1960
45 Chaithiraphan S Goldberg E O Reilly M and Jootar P Multiple aneurysms of coronary artery in sclerodermal heart disease Angiology 24 86 1973
46 Barclay C C Glenney W R Hobbs R E and Bohnenblust W R Aneurysms of the coronary artery A case report Am J Roentgenol 91 1315 1964
47 Ebert P A Peter R H Caulie Cunrels J and Sabiston D Resecting and grafting of coronary artery aneury m Circulation 43 593 1971
48 McMartin D E Stone A J and Franch R H Multiple coronary artery aneurysms in a child with angina pectoris N Engl J Med 290 669 1974
49 Sherkat A Kavanagh Gray D and Edworthy J Localized aneurysms of the coronary arteries, Radiol C 89 74 1967
50 Aintablian A Hamby R I Hoffman I and Kramer R J Coronary ectasia Incidence and results of coronary bypass surgery AM HEART J 96 309 1978
51 Bloch A Dinsmore R F and Lees R S Coronary arteriographic findings in type II and type IV hyperlipoproteinaemia Lancet 1 928 1976

Evaluation of pericardial effusion with computed tomography

Haruo Tomoda, M D *
Mitsumoto Hoshiai M D
Hideo Furuya M D
Yasuaki Oeda M D
Sadatoshi Matsumoto M D
Teruhisa Tanabe M D
Hiromitsu Tamachi M D
Hiroshi Sasamoto M D
Shirosaku Koide M D **
Sachio Kuribayashi M D
Seiya Matsuyama M D * *
Kanagawa Japan

Pericardial effusion has been evaluated noninvasively by the echocardiographic technique or by radioisotope methods [3] However exact information concerning the volume distribution and nature of the pericardial effusion can not be obtained by these methods Although computed tomography has been successfully applied in the evaluation of structural abnormalities of various organs there have been few reports of its application to the diagnosis of heart diseases [4,5]

One of the most important reasons for this appears to be the rapid motion of the heart which hinders adequate delineation of the cardiac structures by conventional computed tomographic systems Although ECG gated methods have been developed [6] our experience does not indicate that the resolution is satisfactory for analysis of cardiac structures [7] On the other hand pericardial effusion appears to be affected less seriously by cardiac motion than other cardiac structures and several reports have indicated the possibility of application of computed tomography for the diagnosis of pericardial effusion [5] Therefore in this report we have attempted to evaluate pericardial effusion with a third generation computed tomographic system

Methods

A computed tomographic three second whole body scanner * which utilized a continuously rotating gantry and pulsed anode with X radiation collimated to form a thin fan-shaped beam was used A complete section was performed in 3 seconds The scale for transparency (CT number) was −1 000 for air 0 for water and +1 000 for bone In the present study no gated tomographic scanning to obtain stop-action images [6] was applied Sustained enhancement was obtained with a rapid intravenous infusion of 200 ml of 30% meglumine iothalamate

The methods were applied to 11 patients with pericardial effusion of various origins (Table I) Pericardial effusion was evaluated independently by conventional ultrasonocardiogram (UCG) methods by one of the authors (M H) on the same day as the tomographic evaluation The computed tomographic findings were assessed without the knowledge of the echocardiographic

From the Department of Cardiology Surgery and Radiology School of Medicin T kai Univ rsity Kanagawa, Japan.

Received f r publication Nov 18, 1979
Accepted f r publication Dec. 19 1979

Reprint req ests Haruo Tomod M.D Department of Cardiol gy (Naika) School f Medicine Tokai University Bosedai, Isehara-shi, Kan gawa ken J pan 259-11
Department of Cardiology School f Medicin Tokai University
Department of Surgery School of Medicine T ka University
Department f Radiology School of Medicine, T kai Uni ersity

* Varian whole body CT scanner

0002-8703/80/060701 + 06$00 60/0 c 1980 The C V Mosby Co



Fig 1 Computed tomographic findings in a normal man RV right ventricle LV left ventricle RA right atrium LA left atrium S interventricular septum *The top of the picture* is the anterior of the patient and *the left* is the patient s right side

findings by two of the authors (S M H T) The volume of pericardial effusion was calculated by measuring pericardial effusion areas on a tomogram and totaling the areas in each tomogram obtained by slicing the heart to a thickness of 1 centimeter Pericardial fluid was collected medically by inserting an 18 gauge polyethylene tube into the pericardial space via the subxyphoid approach in two patients (Cases 1 and 3) and drained surgically by pericardial fenestration in four patients (Cases 8 9 10 and 11) after completion of the computed tomographic and echocardiographic evaluation

Results

Demonstrative cases with pericardial effusion studied with computed tomography are outlined below

Fig 1 shows an enhanced cardiac computed tomogram of a 28 year old man without any cardiovascular abnormalities At a level 7 cm below the sternoclavicular angle the left atrium right atrium left ventricle and part of the right ventricle are revealed *(upper panel) The lower panel* shows tomographic findings at the level of the right and left ventricles The top of the picture is the anterior of the patient and the left shows the patient s right side The atria and ventricles are in close contact with the lungs without any signs of pericardial effusion

Fig 2 was obtained from a 66 year old man (Case 1) with acute viral pericarditis (enhancement was not performed) The tomogram was obtained at a level 10 cm below the sternoclavicular junction The patient was obese and the transparent zone *(F)* surrounding the heart shows a CT number of −39 which is consistent with that of the subcutaneous fat The zone surrounding the area *(F)* which is indicated by *E* had a CT number of +20 which was lower than that of the heart muscle (CT number of +44) and was compatible with pericardial effusion The volume of pericardial fluid calculated by the tomographic technique is 431 ml and 280 ml of the fluid was removed from a canula inserted into the pericardial space via the subxyphoid route (the fluid had a yellowish color and a protein *content of* 4.5 gm /dl)

Fig 3 was obtained from a 66 year old woman with typical signs and laboratory data indicating hypothyroidism (Case 6) The electrocardiogram showed low voltage a chest x ray indicated marked enlargement of the cardiac silhouette and a moderate amount of pericardial effusion was detected by echocardiographic evaluation The tomogram shown in the upper panel of Fig 3 indicated pericardial effusion *(E)* which surrounded the right atrium and ventricles (enhancement was not performed)

The CT number of the pericardial effusion was +28 and that of the left ventricular chamber was +48 Thus x ray transparency of the effusion in hypothyroidism was lower than that observed in the patient with acute pericarditis The volume of the pericardial effusion estimated by tomography was 350 ml *The lower panel* of Fig 3 indicates computed tomographic findings of the same patient as shown in the upper panel but after treatment with a thyroid preparation for 4 months The effusion became clear

Fig 4 is from a 77 year old man with mitral regurgitation (Case 4) As shown in *the upper panel* there was marked cardiomegaly and appar

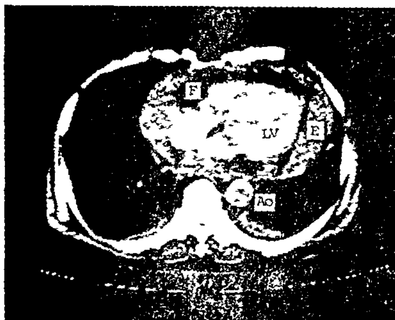


Fig 2 Computed tomographic findings of a patient with acute viral pericarditis LV left ventricle F pericardial fat E pericardial effusion (CT number +20)

Table I Clinical data and computed tomographic findings in patients with pericardial effusion

Patient no	Age sex	Clinical diagnosis	Calculated volume of effusion (ml)	CT number of effusion	Detection by UCG	Collected pericardial fluid		
						Nature	Volume (ml)	Methods
1	66 M	Acute viral pericarditis	431	20	+	Yellowish	280	Medical
2	20 F	Systemic lupus erythematosus	128		+			
3	20 M	Acute viral pericarditis	371	[illegible]0	+	Yellowish	130	Medical
4	77 M	Heart failure	25	13	−			
5	51 F	Renal failure	235	1[illegible]	+			
6	66 F	Hypothyroidism	350	28	+			
7	60 F	Hypothyroidism	[illegible]03	30	+			
8	[illegible]6 F	Carcinoma (breast)	2[illegible]3	13	+	Yellowish	200	Surgical
9	56 F	Carcinoma (pancreas)	379	18	+	Yellowish	300	Surgical
10	58 F	Carcinoma (bronchial)	58[illegible]	40	+	Bloody	5[illegible]0	Surgical
11	31 M	Post cardiac surgery	496	26	+	Semi bloody	400	Surgical

Not measured

ent pleural effusion with possible pericardial effusion As shown in *the lower panel* the computed tomogram at a level 7 cm below the sternoclavicular angle revealed a giant left atrium right atrium aorta right ventricular outflow and pleural effusion A small amount of pericardial effusion (calculated tomographically as 25 ml) was delineated along the right ventricle and the lateral wall of the left atrium The CT number of the pleural and pericardial effusion was +13 This small amount of pericardial fluid could not be detected echocardiographically

Fig 5 is a computed cardiac tomogram of 58 year old woman with shock and paradoxical pulse which were compatible with cardiac tamponade (Case 10) The fluid obtained from area E (pleural effusion) was chylous and the fluid obtained from E_1 (pericardial effusion) was bloody (hemoglobin content = 10 3 gm /dl)

The possibility of an inadequate technique for pericardial fluid sampling could not be ruled out On the other hand x ray transparency of areas E_1 and E was apparently different and the CT number of area E was +40 that of area E was

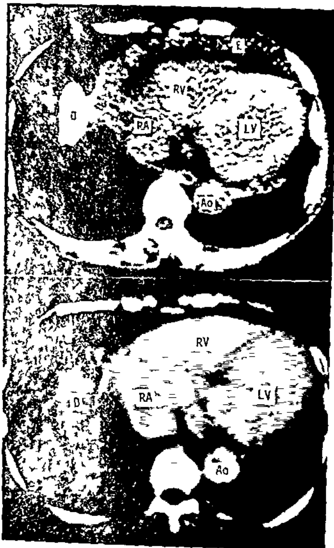


Fig 3 Computed tomographic findings of a woman with hypothyroidism *RA* right atrium *RV* right ventricle *LV* left ventricle *Ao* aorta *D* diaphragm *E* pericardial effusion (CT number +28) *Upper panel* is before treatment and lower panel is after treatment with thyroid preparation

+13 and that of the left ventricle was +44 Thus fluid in the pericardial and pleural cavities appeared to be of different origin The volume of the pericardial effusion calculated tomographically was 585 ml Pericardiectomy was performed to obtain 500 ml of bloody fluid similar to that described above and adenocarcinoma type cells were detected from the specimen Invasion of the bronchial carcinoma into the pericardium and destruction of the thoracic duct were suspected

Data obtained for the rest of the patients are summarized in Table I

The volume of pericardial effusion calculated tomographically was almost compatible with that drained surgically but it was more than the volume of pericardial fluid collected via a tube inserted into the pericardial [illegible]

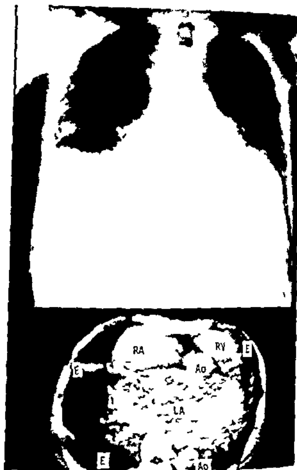


Fig 4 Computed tomographic findings of a man with mitral regurgitation during bilateral heart failure *RA* right atrium *RV* right ventricle *Ao* aorta *LA* left atrium *E* pleural and pericardial effusion (CT number +13)

Detection of the pericardial effusion was possible by echocardiography except in Case 4 with a small amount of localized pericardial fluid as illustrated in Fig 4

The CT number was high in bloody pericardial effusion (+40 in Case 10 +26 in Case 11) low in renal or heart failure (+13 in Case 4 +12 in Case 5) relatively high in hypothyroidism (+28 in Case 6 +30 in Case 7) and relatively low in the rest of the patients

Discussion

Echocardiography[1,2] and radioisotopic methods[3] are the two most popular noninvasive methods for evaluation of pericardial effusion However computed tomography offers not only information on the fluid volume and its distribution but also on the gross nature of the fluid from the difference in x ray transparency—i e the difference in the CT numbers According to our experience on a limited number of patients x ray transparency was high in pericardial effusion due

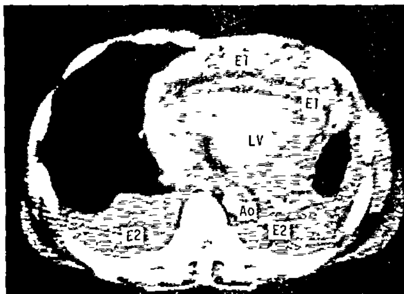


Fig 5 Computed tomographic findings of a woman with clinical signs of cardiac tamponade due to invasion of bronchial carcinoma *LV* left ventricle (CT number +44) *Ao* aorta E_1 pericardial effusion (hemorrhagic CT number +40) E_2 pleural effusion (chylous CT number +13)

to renal or heart failure non hemorrhagic carcinomatous invasion acute viral pericarditis myxedema and hemorrhagic pericardial fluid in that order When the pericardial effusion was whole blood logically the effusion could not be differentiated from the left ventricular cavity filled with blood When the pericardial effusion was mixed with blood as in Cases 10 and 11 x ray transparency was higher than that of whole blood and lower than that of the exudate or transudate and the CT numbers depended on the amount of the blood contained in the pericardial fluid Normally pericardial fluid due to myxedema was not aspirated but previous studies indicated that the fluid contained a high value of cholesterol [1] and this might be the reason for the relatively high CT numbers of the pericardial fluid in hypothyroidism

The volume of pericardial fluid calculated by tomographic methods was almost consistent with the volume drained surgically but more than that aspirated by inserting a small gauge tube most probably due to the fact that complete aspiration of the fluid was not possible by the latter technique

Evaluation of the presence and gross volume of pericardial fluid was possible echocardiographically in 10 out of 11 patients in the present study However computed tomographic methods appear to be more sensitive concerning the minimum volume of pericardial effusion to be detected especially when it is localized as illustrated in Fig 4

The stop action method gated with ECG was possible with the system used in the present study [6] but our impression is that the quality of the tomogram is not satisfactory because of reduced data sampling numbers for every frame of the tomogram

Without gating the effectiveness of CT scan in heart disease is limited to global diagnosis Therefore delineation of the pericardial effusion is an adequate indication of computed tomographic applications in cardiology at present although effects of exaggerated heart movement in the pericardial fluid due to the lack of fixation of the heart by the pericardium should be taken into consideration [2]

Summary

Evaluation of pericardial effusion was attempted with computed tomography in 11 patients The volume and distribution of pericardial fluid were assessed with satisfactory resolution and the nature of the fluid was estimated by the difference in x ray transparency (CT numbers) The volume of pericardial fluid calculated by tomographic methods ranged from 25 ml to 585 ml and agreed well with the surgically drained fluid volume The CT numbers of the pericardial effusion due to renal or heart failure acute viral pericarditis hypothyroidism and

hemopericardium were +12 to +13 +20 +28 to +30 and +26 to +40 respectively Therefore the volume and gross nature of the pericardial fluid could be estimated noninvasively with computed tomography

REFERENCES

1 Feigenbaum E H Echocardiographic diagnosis of pericardial effusion, Am. J Cardiol. 26 475 1970
2. Tanaka M Kosaka S Terasawa Y Kashiwagi, M and Meguro T Morphological and dynamical characteristics of the heart in pericardial effusion Cardiovasc Sound Bull. 5 3 1975
3 Kriss, J P Acquired cardiovascular disease—pericardial effusion in Quantitative Nuclear Cardiology editor Pierson R N New York 1975 John Wiley & Sons p 117
4 Wood E H New vistas for the study of structural and functional dynamics of the heart lungs and circulation by non invasive numerical tomographic vivisection Circulation 56 506 1971
5 Huang H K and Mazziotta J C Heart imaging computerized tomography Computerized Tomogr 2 37 1978
6 Harell G S Guthaner D F Breiman R S Morehouse C C Seppi E J., Marshall W H Jr and Wexler L Stop action cardiac computed tomography Radiology 123 515 1977
7 Tomoda H Kuribayashi, S and Matsuyama, S Evaluation of cardiovascular diseases with computed tomography J Cardiography 9 409 1979
8 Masuda Y Watanabe S Inagaki Y Uchiyama, G. Arimizu N., Tateno Y and Watanabe E. Cardiac images by computed tomography employing JOEL dynamic scanner (in Japanese) Kokyu to Junkan 26 439 1978
9 Alfidi, R J McIntyre W J., Meaney T F Chernak E S Janicki P Tarar R and Levin H Experimental studies to determine application of CAT scanning to the human body Am J Radiol. 124 199 1975
10 Davis P J and Jacobson S Myxedema with cardiac tamponade and pericardial effusion of gold paint appearance Arch Intern Med 120 165 1967

Distribution and severity of left ventricular wall motion abnormalities according to age and coronary arterial pattern in 500 patients with coronary artery disease and angina pectoris*

W V R Vieweg CAPT MC USN
J S Alpert MD
A D Johnson MD
G W Dennish MD
D P Nelson LCDR MSC USN
S E Warren LCDR MC USN
A D Hagan CAPT MC USN
San Diego and La Jolla Calif and Worcester Mass

The influence of age and coronary arterial pattern on left ventricular function has not been studied systematically in patients with coronary artery disease and angina pectoris. Since the adverse effects of atheromatous coronary artery disease on left ventricular performance tend to be progressive, it might be expected that different distributions or severity of left ventricular wall motion abnormalities would be encountered in patients of different ages with symptomatic coronary artery disease. Furthermore, specific coronary arterial patterns of Right, Mixed, and Left systems might also influence the distribution and severity of left ventricular wall motion abnormalities as a result of differing distributions of myocardial blood flow. Therefore we undertook a meticulous review of coronary arterial anatomy and distribution and severity of left ventricular wall motion abnormalities in 500 patients who underwent coronary arteriography and left ventriculography for evaluation of angina pectoris.

Methods

The coronary arteriograms and left ventriculograms of 500 patients with coronary artery disease and angina pectoris studied between 1972 and 1977 were reviewed carefully by three physicians. When differences existed in the interpretation of this material, a consensus was reached. Such differences were rare and minor in nature. Patients with coronary arterial anomalies, congenital heart disease, valvular heart disease, or primary heart muscle disease were excluded. All patients had at least one lesion of greater than 50% reduction of luminal diameter in a major coronary artery.

Ninety five percent of the studies were performed percutaneously from the leg; the remainder were performed using a cutdown in the arm. The left ventriculograms were exposed on 35 mm film at 60 frames/second in the right anterior oblique projection using a Philips 9 inch cesium iodide image intensifier system (Philips Medical Systems Inc, Shelton, Conn.). Only films of excellent quality and frames removed from ectop

From the Cardiology Branch, Department of Medicine, and the Clinical Investigation Center, Naval Regional Medical Center, San Diego, Calif; the Division of Cardiovascular Medicine, Department of Medicine, University of Massachusetts, Worcester, Mass.; and the Division of Cardiology, Department of Medicine, School of Medicine, University of California San Diego, La Jolla; and the Veterans Administration Hospital, La Jolla, Calif.

Supported in part by Bureau of Medicine and Surgery Clinical Investigation Program Project 8 16 1139.

Received for publication Oct 1, 1979.

Accepted for publication Jan 10, 1980.

Reprint requests: CAPT W V R Vieweg, MC, USN, Cardiology Branch, Naval Regional Medical Center, San Diego, Calif 9 134.

*The opinions or assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the Navy Department or the naval service at large.

000?-8 03/80/060/07 + 07$00 ?0/0 © 1980 The C V Mosby Co

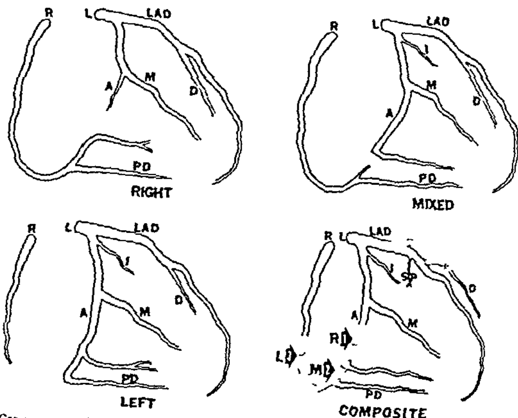


Fig 1 Coronary arterial patterns divided into Right Mixed and Left systems according to the blood supply to the inferior surface of the left ventricle. "Breaks" in the composite diagram show how each coronary arterial pattern is formed. (P 1 = Right system M 2 = Mixed system and L-3 = Left system) Abbreviations R = right L = left LAD = left anterior descending D = diagonal SP = septal perforator I = intermediate M = marginal ... atrioventricular groove PD = posterior descending

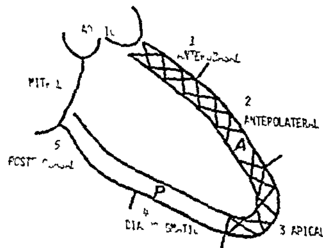


Fig 2 Left ventriculogram in the right anterior oblique projection. The left ventricle has been divided into anterior (A) and posterior (P) regions and into five areas

ic beats by at least two cardiac cycles were evaluated Forty five cc of meglumine diatrizoate were introduced into the left ventricle in three seconds using a power injector

Coronary arterial patterns were divided into Right Mixed, and Left systems depending upon the blood supply to the inferior surface of the left ventricle (Fig 1) In Right systems the right coronary artery (RCA) supplies the posterior descending artery and the posterolateral artery In Mixed systems the RCA supplies the posterior descending artery and the atrioventricular groove artery (AV groove artery) supplies the posterolateral artery In Left systems the RCA terminates at the acute margin of the right ventricle and the AV groove artery supplies the posterolateral artery and the posterior descending artery

The left ventriculograms in the right anterior oblique projection were divided into five areas (1 anterobasal 2 anterolateral 3 apical 4-diaphragmatic and 5 posterobasal) and two regions (anterior and posterior) (Fig 2) A scoring system was employed for each area (normal = 0 hypokinesis = 1 akinesis = 2 and dyskinesis = 3) ... then the left ventriculograms were divided into four categories depending upon regional involvement (1) normal (2) anterior dyssynergy ...

Table I Wall motion findings by system and age (± standard deviation) in 500 patients with angina pectoris

	Anterior dyssynergy	*Posterior dyssynergy*	*Anterior & posterior dyssynergy*	*Normal*
Right system (360 pts)	49 4 ± 9 1 years 66 patients (18%)	48 8 ± 10 8 years 76 patients (19%)	50 1 ± 11 2 years 68 patients (19%)	49 5 ± 9 0 years 150 patients (42%)
Mixed system (89 pts)	45 1 ± 8.9 years 16 patients (18%)	47 [illegible] ± 10 2 years 14 patients (16%)	49 6 ± 10 0 years 18 patients (20%)	48 [illegible] ± 8 1 years 41 patients (46%)
Left system (51 pts)	48 9 ± 10 1 years 17 patients (33%)	45 0 ± [illegible]3 years 9 patients (18%)	50 8 ± 3.9 years 9 patients (18%)	50 6 ± 10 6 years 16 patients (31%)
Total (500 pts)	48 6 ± 9 3 years 99 patients (20%)	48 3 ± 10 4 years 99 patients (20%)	49.9 ± 10.5 years 95 patients (19%)	49.5 ± 8 9 years [illegible]07 patients (41%)

(3) posterior dyssynergy alone and (4) combined anterior and posterior dyssynergy

Statistical comparisons of mean age for each wall motion group in Table I with the over all mean age of all 500 patients were made by standardized Z score assuming normal age distributions and equal variances The frequency and type of dyssynergy observed for the three coronary arterial systems (Table IV) and ages (Table V) were compared with the over all distribution of dyssynergy by contingency analysis using 2 × 3 tables The resulting Chi square with 2 degrees of freedom determined the probability of distinct differences between coronary arterial systems or decades of life

Results

The mean age of the 437 men was 48 5 years and the mean age of the 63 women was 53 6 years In analyzing wall motion by coronary arterial system and age (Table I) men and women were combined The mean age for the entire study group (49 1 ± 9 61 years) was compared to each of the subcategories in Table I to determine whether either coronary arterial system or location of dyssynergic area occurred in a distinct age group The standardized normal deviate Z was computed from the means and standard deviations of the complete group and was compared to those of the individual elements Only in the case of Left systems did the standard deviations fall outside the expected 9 to 11 range for two categories with only nine patients (Table I) In no instance was the p value computed for differences between means significant at the 0 05 level even for the small samples It was concluded therefore that coronary arterial system and distribution of left ventricular dyssynergic regions are independent of age

Table II defines left ventricular wall motion dyssynergy by coronary arterial system (Right Mixed and Left) region (anterior dyssynergy alone posterior dyssynergy alone or combined anterior and posterior dyssynergy) and area (1 anterobasal 2 anterolateral 3 apical 4 diaphragmatic and 5 posterobasal) In all systems and regions and in all areas save apical hypokinesis was the dominant left ventricular wall motion abnormality In case 3 (apical) dyskinesis was the dominant finding

Patients with dyssynergy were then evaluated for extent (number of areas involved) of abnormal wall motion (Table III) In patients with anterior regional disease (anterior dyssynergy alone or combined anterior and posterior dyssynergy) areas 2 (anterolateral) and 3 (apical) together were impaired most commonly Rarely all three anterior areas were involved Dyssynergy was never seen in combined areas 1 and 2 or in areas 1 and 3 In posterior regional involvement the combinations of areas 4 and 5 together or area 4 alone occurred with similar frequency It was uncommon for area 5 alone to be involved

The frequency of occurrence of the three types of wall motion abnormality (hypokinesis akinesis and dyskinesis) in the entire group of 500 patients (Table IV) was compared with the distribution of left ventricular dyssynergy within the

Table II Wall motion dyssynergy by system region and area

	H	A	D	Total	H	A	D
Right system							
Anterior							
Area 1	1	0	0	1	100%	0%	0%
Area 2	39	4	11	54	72%	[illegible]	20%
Area 3	16	10	21	47	34%	21%	45%
Posterior							
Area 4	39	23	4	66	59%	35%	6%
Area 5	25	14	5	44	57%	32%	11%
Anterior & Posterior							
Area 1	4	0	0	4	100%	0%	0%
Area 2	41	12	5	58	71%	21%	9%
Area 3	21	4	35	60	35%	7%	58%
Area 4	43	18	3	64	67%	28%	5%
Area 5	27	11	4	42	64%	26%	10%
Total	256	96	88	440			
Mixed system							
Anterior							
Area 1	0	0	0	0	0%	0%	0%
Area 2	10	1	3	14	71%	7%	21%
Area 3	[illegible]	0	6	13	54%	0%	46%
Posterior							
Area 4		3	0	10	70%	30%	0%
Area 5		1	1	9	78%	11%	11%
Anterior & Posterior							
Area 1	1	0	0	1	100%	0%	0%
Area 2	9	1	5	15	60%	7%	33%
Area 3	7	0	10	17	41%	0%	59%
Area 4	11	5	2	18	61%	28%	11%
Area 5	5	2	1	8	63%	25%	13%
Total	64	13	28	105			
Left system							
Anterior							
Area 1	0	0	0	0	0%	0%	0%
Area 2	10	4	2	16	63%	25%	13%
Area 3	4	1	8	13	31%	8%	62%
Posterior							
Area 4	6	1	1	8	[illegible]	13%	13%
Area 5	4	0	2	6	67%	0%	33%
Anterior & Posterior							
Area 1	0	0	0	0	0	0%	0%
Area 2	5	0	3	8	63	0%	38%
Area 3	3	0	5	8	[illegible]	0%	63%
Area 4	5	1	3	9	[illegible]	11%	33%
Area 5	0	1	2	3	[illegible]	33%	67%
Total	37	[illegible]	[illegible]	[illegible]			

Abbreviations H = hypokinesis A = [illegible] [illegible] kinesis

Table III Extent of wall motion abnormalities according to coronary arterial system and degree of involvement wall motion abnormalities were divided into three categories anterior alone posterior alone and combined anterior and posterior

	Right system	Mixed system	Left system	Total
Anterior				
Area 1 2 3	0	0	0	0
Area 1 2	0	0	0	0
Area 1 3	0	0	0	0
Area 2 3	36	11	17	[illegible]
Area 1	1	0	0	1
Area 2	18	3	4	25
Area 3	11	2	1	[illegible]
Posterior				
Area 4 5	34	5	5	44
Area 4	[illegible]	5	3	40
Area 5	10	4	1	15
Anterior & Posterior				
Area 1 2 3	4	1	0	5
Area 1 2	0	0	0	0
Area 1 3	0	0	0	0
Area 2 3	47	13	[illegible]	[illegible]
Area 1	0	0	0	0
Area 2	8	1	1	10
Area 3	10	3	1	13
Area 4 5	38	8	3	[illegible]
Area 4	26	10	6	[illegible]
Area 5	4	0	0	4

three coronary arterial systems Right and Mixed systems did not differ significantly from the over all distribution Patients with Left systems did demonstrate a significant departure from the population as a whole ($p < 0.05$) although the number of observations in this group is small A similar analysis (Table V) was conducted for the distribution of left ventricular wall motion abnormalities according to decades of life compared with the entire population No age group differed from the over all population (0 05 level of significance) Thus it appears that the distribution of wall motion abnormalities in patients with coronary artery disease and angina pectoris is similar from the third to the eighth decade

Using the scoring system described in the Methods section as an index of the severity of left ventricular dyssynergy the mean wall motion scores per patient for coronary arterial system

Table IV Comparison of wall motion findings by coronary arterial system

	H	A	D	Total score	Score per patient with dyssynergy (± standard deviation)/per dyssynergic area
Right systems (?10 to 360 patients had dyssynergy)	256 × 1	96 × 2	88 × 3	71[illegible]	3 4 ± 2 2/1 6
Mixed systems (48 of 89 patients had dyssynergy)	64 × 1	13 × 2	?8 × 3	174	3 6 ± 2 5/1 7
Left systems (35 of 51 patients had dyssynergy)	37 × 1	8 × 2	26 × 3	131	3 ± 2.2/1.8
Total	357 × 1	117 × 2	142 × 3	1 017	3 5 ± 2.2/1 7

For scoring purposes hypokinesis (H) = 1 akinesis (A) = 2 and dyskinesis (D) = 3

Table V Comparison of wall motion findings by decade

Decade	H	A	D	Total score	Score per patient with dyssynergy (± standard deviation)/per dyssynergic area	Patients without dyssynergy
20 29 (8 pts)	11 × 1	5 × 2	5 × 3	36	5 1 ± 2.5/1 7	1 (1?%)
30 39 (80 pts)	6? × 1	14 × 2	14 × 3	132	2 6 ± 1 7/1 5	29 (?%)
40-49 (166 pts)	119 × 1	35 × 2	55 × 3	3?4	3 8 ± ?5/1 7	73 (?6%)
50 59 (174 pts)	113 × 1	44 × 2	49 × 3	348	3 4 ± ?0/1 ?	73 (42%)
60 69 (6? pts)	45 × 1	17 × 2	16 × 3	1?7	3.5 ± 2 4/1 6	29 (4?%)
?0 79 (7 pts)	7 × 1	2 × 2	3 × 3	?0	4 0 ± 2.3/1 7	2 (29%)
Total (500 pts)	3?7 × 1	117 × 2	14? × 3	1 01?	3.? ± ?.2/1 ?	207 (41%)

For scoring purposes hypokinesis (H) = 1 akinesis (A) = 2 and dyskinesis (D) = 3

(Table IV) and age (Table V) were compared with the mean score (3 5 ± 2 2) of the entire population None of the arterial systems had scores which differed significantly from the over all mean population (p > 0 1) Among decades of life only patients in the fourth decade differed significantly from the mean score for the entire population Thus there is little difference in the severity of left ventricular dyssenergy according to age

Discussion

The severity of coronary artery disease and the degree of left ventricular dysfunction determine the clinical presentation and natural history of patients with ischemic heart disease[2] This study concentrates on a detailed description of left ventricular wall motion findings in patients with coronary artery disease and angina pectoris

In selecting the right anterior oblique projection for analysis of the left ventriculogram the septum and lateral wall are not seen well However disease confined to the septum or lateral wall is very rare In one study of 78 separate infarctions only two infarctions were limited to the septum while three infarctions were limited to the lateral wall[4] Some portion of the anterior wall is involved almost invariably in patients with septal infarction since the left anterior descending artery supplies the anterior wall of the left ventricle as well as 75% of the interventricular septum In lateral wall infarction there is almost always anterior or posterior involvement Thus the single plane right anterior oblique ventriculogram should be adequate for characterization and comparison of left ventricular wall motion abnormalities

Some wall motion abnormalities are the result of ischemia and are therefore potentially reversible thereby eliminating a one to one relationship between findings at the time of left ventriculography and at autopsy[5-7] However left ventricular disease found at autopsy is commonly associated

with antemortem left ventricular dyssynergy[8]

The descriptive concepts of hypokinesis akinesis and dyskinesis have the advantages of both long term use[1] and wide acceptance[9] The division of the left ventricle into anterior and posterior regions has been validated recently[4, 10, 11]

The distribution of anterior and posterior left ventricular disease was equally divided in our population (Table I) a finding observed by others[12] Combined anterior and posterior dyssynergy occurred with no greater frequency than anterior or posterior dyssynergy alone in our patients The even distribution of regional wall motion abnormalities was not influenced by coronary arterial pattern (Tables I and IV) This is in contrast to Schlesinger s observations[13] that patients with Left systems were most vulnerable and those with Mixed systems were least vulnerable to the effects of coronary artery disease

Hypokinesis was the most common wall motion abnormality found This was true in all areas of the left ventricle except for area 3 (apical), where dyskinesis was found most frequently (Table II) Miller and colleagues[14] also noted that hypokinesis was the most common wall motion abnormality in patients with coronary artery disease[14] Of their 123 patients 32% were normal 30% manifested hypokinesis 21% manifested akinesis and 17% manifested dyskinesis

Dyssynergy occurred most commonly in adjacent areas (Table III) In patients with anterior wall dyssynergy areas 2 (anterolateral) and 3 (apical) together were involved most commonly This supports observations that anterior myocardial infarctions tend to be apical rather than basal in orientation [11] In patients with posterior wall dyssynergy areas 4 (diaphragmatic) and 5 (posterobasal) together were involved most frequently

The most interesting finding in our data was the demonstration that wall motion abnormalities were similar in each decade of life studied (Table V) One might expect to find progressive deterioration of left ventricular function as one moves from younger to older patients since age is a well known risk factor for coronary artery disease However the common denominator in this population was angina pectoris It may be that when coronary artery disease with its attendant impact on left ventricular function expresses itself clinically, the disease is sufficiently advanced so than any implications of age are removed

Conclusions

1 Forty % of patients with coronary artery disease and angina pectoris have normal left ventricular wall motion In the 60% of patients with left ventricular dyssynergy wall motion abnormalities are divided evenly into three categories anterior dyssynergy alone posterior dyssynergy alone and combined anterior and posterior dyssynergy The mean age of patients with normal and dyssynergic wall motion is strikingly similar

2 Coronary arterial patterns of Right Mixed, and Left systems have little if any influence on left ventricular wall motion abnormalities

3 Hypokinesis is the most common wall motion abnormality found in patients with coronary artery disease regardless of coronary arterial distribution or region of the left ventricle affected with the exception of the apical area, where dyskinesis is found most commonly Dyssynergy occurs most commonly in adjacent areas In anterior wall dyssynergy the anterolateral and apical areas of the left ventricle are involved together most commonly In posterior wall dyssynergy the diaphragmatic and posterobasal areas of the left ventricle are involved most commonly

4 In patients with coronary artery disease and angina pectoris left ventricular dyssynergy is similar from the third to the eighth decade of life

Summary

Left ventriculograms of 500 patients with coronary artery disease and angina pectoris were compared with respect to coronary arterial pattern left ventricular dyssynergy and the patient s age The coronary arterial patterns were separated into Right Mixed and Left systems depending upon the blood supply to the inferior surface of the left ventricle The left ventriculograms were divided into two regions and five areas The anterior region consisted of the anterobasal area anterolateral area and the apical area The posterior region consisted of the diaphragmatic area and the posterobasal area Areas were scored as normal hypokinetic akinetic or dyskinetic The following relationships were noted

1 Forty percent of patients with coronary artery disease and angina pectoris have normal left ventricular wall motion In the 60% of patients with left ventricular dyssynergy wall motion abnormalities are divided evenly into three categories anterior dyssynergy alone posterior dyssynergy alone and combined anterior and posterior dyssynergy The mean age of patients with normal and dyssynergic wall motion is strikingly similar

2 Coronary arterial patterns of Right Mixed and Left systems have little if any influence on left ventricular wall motion abnormalities

3 Hypokinesis is the most common wall motion abnormality found in patients with coronary artery disease regardless of coronary arterial distribution or region of the left ventricle affected with the exception of the apical area where dyskinesis is found most commonly Dyssynergy occurs most commonly in adjacent areas In the anterior wall dyssynergy the anterolateral and apical areas of the left ventricle are involved together most commonly In posterior wall dyssynergy the diaphragmatic and posterobasal areas of the left ventricle are involved most commonly

4 In patients with coronary artery disease and angina pectoris left ventricular dyssynergy is similar from the third to the eighth decade of life

REFERENCES

1. Herman, M V, Heinle R. A., Klein M D and Gorlin, R. Localized disorders in myocardial contraction Asynergy and its role in congestive heart failure N Engl J Med. 277 222 1967
2. Bruschke A G., Proudfit W L., and Sones, F M Jr Progress study of 590 consecutive nonsurgical cases of coronary disease followed 5-9 years. I Arteriographic correlations Circulation 47 1147 1973
3. Bruschke A G., Proudfit W L. and Sones, F M., Jr Progress study of 590 consecutive nonsurgical cases of coronary disease followed 5-9 years II. Ventriculograph ic and other correlations, Circulation 47 1154 1973
4. Sullivan, W., Vlodaver Z., Tuna, N., Long L. and Edwards J E Correlation of electrocardiographic and pathologic findings in healed myocardial infarction Am. J Cardiol. 42 724 1978
5. Pasternac, A., Gorlin, R., Sonnenblick, E. H., Haft J I., and Kemp H G Abnormalities of ventricular motion induced by atrial pacing in coronary artery disease Circulation 45 1195 1972.
6. Cohn P F., and Gorlin, R. Abnormalities of left ventricular function associated with the anginal state Circulation 46 1065 1972.
7. Banka, V S., Bodenheimer M M., and Helfant, R. H Determinants of reversible asynergy The native coronary circulation Circulation 52 810 1975
8. Hutchins, G M., Bulkley B H., Ridolfi, R. L., Griffith, L. S C., Lohr F T., and Piasio M A. Correlation of coronary arteriograms and left ventriculograms with postmortem studies, Circulation 56 32 1977
9. Austen, W G., Edwards, J E., Frye R. L., Gensini, G G., Gott V L., Griffith, L. S C., McGoon, D C., Murphy M L., and Roe B B A reporting system on patient evaluated for coronary artery disease Report of the Ad Hoc Committee for Grading of Coronary Artery Disease Council on Cardiovascular Surgery American Heart Association Circulation (IV) Suppl 5-40 1975
10. Roberts W C., and Gardin, J M Location of myocardial infarcts A confusion of terms and definitions, Am. J Cardiol. 42 868 1978
11. Savage R. M Wagner G S., Ideker R. E., Podolsky S A., and Hackel D B Correlation of postmortem anatomic findings with electrocardiographic changes in patients with myocardial infarction. Retrospective study of patients with typical anterior and posterior infarcts Circulation 55 279 1977
12. Barnes A. R. Electrocardiogram in myocardial infarction. Review of one hundred and seven clinical cases and one hundred and eight cases proved at necropsy Arch. Intern. Med 55 457 1935
13. Schlesinger M J Relation of anatomic pattern to pathologic conditions of the coronary arteries Arch. Pathol. 30 403 1940
14. Miller R. R., Amsterdam, E. A., Bogren H. G., Massumi, R. A., Zelis R., and Mason, D T Electrocardiographic and cineangiographic correlations in assessment of the location nature and extent of abnormal left ventricular segmental contraction in coronary artery disease Circulation 49 447 1974

Effects of induced psychological stress on click and rhythm in mitral valve prolapse

Robert L Combs M D
Pravin M Shah M D
Rhonda S Klorman Ph D
Rafael Klorman Ph D
With the technical assistance of Linda J Sylvester
Rochester N Y

The variability of ausculatory findings in patients with mitral valve prolapse (MVP) has been extensively studied Changes in the timing of the click and murmur on a repeat examination and with respiration and other physiologic (e g sitting standing squatting Valsalva maneuver) and pharmacologic (e g amyl nitrite pressors) maneuvers have received considerable attention However a few studies have also examined the amplitude of the click in a similar fashion Our clinical observations suggested that anxiety tended to accentuate the click in patients with MVP The present study was designed to examine the effects of anxiety on the auscultatory features of MVP In addition since atrial and ventricular rhythm disturbances are common in this condition it was hypothesized that anxiety might exacerbate these dysrhythmias Thus during the administration of acute psychological stress designed to induce anxiety the rhythm was monitored and the phonocardiogram (PCG) was recorded This preliminary report shows that some patients with the systolic click murmur syndrome are profoundly affected by such a stress

From the Cardiology Unit Departments of Medicine Psychiatry and Psychology University of Rochester Rochester N Y

This study was supported in part by the National Institutes of Health Training Grant HL 0 00 for the National Heart and Lung Institute

Received for publication Oct 10 1979

Accepted for publication Dec 3 1979

Reprint requests Pravin M Shah M D Cardiology D n Wadsworth VA Medical Center Wilshire and Sawtelle Blvd Los Angeles Calif 90073

Materials and methods

The present study group was composed of 30 subjects—15 patients and 15 controls All patients had clinical features of the systolic click murmur syndrome Each patient had auscultatory evidence (confirmed by phonocardiography) of a late systolic click which varied in timing with the bedside maneuvers designed to change ventricular volume All had been studied by echocardiography and MVP was confirmed in 11 patients The four patients without echocardiographic confirmation had the characteristic auscultatory features None had evidence of other cardiac disease The control subjects matched by age and sex had no evidence of heart disease

Informed consent was obtained prior to the study As shown in Fig 1 subjects remained semirecumbent in an easy chair during the entire study A single electrocardiographic (ECG) lead was continuously monitored A microphone was placed over the cardiac apex where sounds were best recorded The microphone was secured to the chest with a rubber strap and tape so that it was held motionless throughout the experiment All ECG and PCG recordings were made on a Cambridge multichannel recorder The sound recordings were made after filtration through a 100 c 250 Hz high pass filter with 24 db per octave roll off Once set the controls were not changed during the entire study The paper speed f continuous recording was 5 mm /second and was increased to 50 mm /second for ten to 15 seconds at the end of each minute Thus the rhythm could be evaluated continuously throughout th

0002 8703/80/060714 + 08$00 80/0 © 1980 The C V Mosby C



Fig 1 Subject shown viewing slide projector (for amplification see text)

experiment and the amplitude and timing of the click could be analyzed each minute during the fast paper speed

A rest period was followed by three different tests periods (practice Task I Task II) The three test periods constituted the psychological stress which was deemed to be sufficiently intense for experimental purposes while still within ethical boundaries Patient anxiety was assessed at three points in the study—After rest after Task I and after Task II The State Trait Anxiety Inventory (STAI) developed by Spielberger and associates[18] was employed for this During the rest period the subjects lay quietly During the test periods serial guessing tasks were administered on a Singer Caramate slide projector During the initial explanation of the test in an effort to intensify the anxiety response it was implied that the accuracy of sequence guessing is a measure of intelligence In each of the three tests the subject was asked to recognize and retain a sequence of the letters X and O which was repeatedly projected The sequence for each test is illustrated in Fig 2 A letter was projected and then removed from the screen[19] When the letter was removed the subject was expected to guess the next letter A correct response was predicated on recognition and memorization of the sequence The responses were recorded on the Cambridge multichannel recorder with hand held buttons marked X and O and therefore no talking was required

RECURRING LETTER SEQUENCE IN THE THREE TESTS

Practice	XXOO
Task I	XOOO
Task II	O X O O X O X O X O X X O X O O X X O X

Fig 2 Recurring letter sequence in the three tests.

During the practice test slides were advanced manually and this period was used to familiarize the subject with the testing technique Practice was terminated when the subject accurately guessed eight consecutive letters In Task I and Task II the slides were advanced automatically at a preset rate Task I was terminated after eight consecutive correct guesses Task II the 20 letter sequence which was essentially unachievable was projected three times—and no subject mastered the pattern The average total duration of each test which included both explanation and actual testing was rest—7 minutes (range 5 to 11 minutes) practice—5 minutes (range 2 to 13 minutes) Task I—6 minutes (range 3 to 9 minutes) and Task II—9 minutes (range 7 to 13 minutes)

The STAI administered during the study is composed of two separate subjective scales for measuring two distinct anxiety concepts The

Table I Patients

Patient	*Age*	*Sex*	*N E.X*	*S.M*	*Prolapse on echo*	*Drugs*	*Rhythm change during test*	*X change during test*
Group A								
J F	45	F	+	+	Yes	Prop 80 qd.	New multifocal VEB s	Increase
E C	41	F	+	+	No	None	New CSR	Increase
L W	49	F	+	+	Yes	None	New VEB s	Increase
J W	18	F	+	–	Yes	None	New multifocal VEB s	Increase
M A	51	M	+	+	Yes	None	Increased VEB s	No
I G	37	M	+	–	No	None	No	Increase
Group B								
N G	25	F	+	+	Yes	None	No	Decrease
V F	57	M	+	+	Yes	None	No	Decrease
S D	36	F	+	+	Yes	Quinidine 800 qd	No	No
[illegible] Y	32	F	+	–	Yes	Prop 160 qd	No	No
I M	32	F	+	–	No	Prop 80 qd	No	No
P C	41	F	+	+	Yes	Prop 20 qd Meprobamate 200 qd	No	No
I W	52	F	+	+	Yes	None	No	No
F B	49	M	+	–	Yes	None	No	No
K B	25	F	+	–	No	None	No	No

Table II Heart rates (Average ± S E M)

	Rest	*Practice*	*Task I*	*Task II*
All patients (15)	72.27 ± 44	76 13 ± .51	78.95 ± 48	8.8[illegible] ± [illegible]
Group A patients (6)	74.58 ± 88	80 62 ± .98	84 85 ± .96	83 85 ± [illegible]
Group B patients (9)	69 06 ± 45	73 14 ± .56	75 01 ± 54	[illegible]5.56 ± 41
Controls (15)	75.55 ± 48	80 74 ± .56	82.33 ± .53	81.38 ± [illegible]

A Trait scale consists of 20 questions about the subject s general level of anxiety The A State scale consists of 20 questions designed to indicate a subject s level of anxiety at a given moment in time Both were given after rest and then A State was given alone after Task I and Task II

The subjects were debriefed on completion of the study emphasizing that they were not expected to correctly guess the sequence of Task II They were then told that the purpose of the tests had been to create psychological stress with a frustrating experience The entire study was completed in 30 to 45 minutes

From the continuously recorded single lead ECG the rhythm was analyzed over each one minute period and arrhythmias were noted If ventricular ectopic beats (VEB s) were observed their frequency was reported each minute as a projected rate per 1 000 heart beats For each of the four periods (rest practice Task I and Task II) a mean of these minute values for VEB frequency was computed The rhythm during rest was compared to that of each of the three test periods

At the end of each minute during the faster paper speed (50 mm /sec) the R R interval over five consecutive cycles was averaged to compute the heart rate In addition amplitude of the click was measured during the fast paper speed The amplitude for a given minute was obtained by averaging the clicks in five consecutive beats All VEB s and post ectopic beats were excluded from analysis of the clicks In addition clicks were not analyzed when obscured by patient noise (talking movement deep breathing) Thus during some minutes no value for amplitude of the click was available Any gross change in timing of the click was also noted The amplitude during rest was compared to that of each of the three test periods A click was considered to have changed if its amplitude during a test period differed from its amplitude during rest by 50% or more

Table III State anxiety scores (Average ± S E M)

	Post rest	*Post Task I*	*Post Task II*
All patients (15)	33 ± 2 1	36 ± 2 6	41 ± 2 1
Group A patients (6)	36 ± 3.6	34 ± 3 6	39 ± 2 7
Group B patients (9)	32 ± 2.5	37 ± 3 6	42 ± 3 2
Controls (15)	29 ± 1 0	33 ± 2 2	39 ± 2 4

Statistical evaluations were made using chi square analyses and two tailed x tests

Results

Patient characteristics are outlined in Table I There were 11 females and four males with a mean age of 39 years (range 18 to 57 years) The controls were comparable with the same sex distribution and a mean age of 40 years (range 21 to 54 years)

Patients were separated into two groups depending on their response to the psychological stress In Group A are six patients who showed either a change in rhythm and/or an increase in amplitude of the click from the rest to a test period Group B is composed of nine patients who showed no change in rhythm and in whom the click did not increase in amplitude

The cardiac rhythm changed during nine test periods in five of 15 patients The arrhythmias consisted of new VEB s in three increased VEB s in one and a new AV nodal (junctional) rhythm in one In the four patients with VEB s the frequency changed from rest period values of 0 0 0 and 173 (VEB s/1 000 beats) to test period values of 4 18 277 and 312 respectively No control subject had a rhythm disturbance during administration of the test ($p < 025$ by chi square test) and the only arrhythmia noted in this group was a single VEB in one subject during rest

Fig 3 illustrates the changes in amplitude of the clicks in individual patients As shown the click increased by 50% or more in five patients in Group A and decreased by this amount in two of the Group B patients

Heart rate data are depicted in Table II In all groups there was an increase in heart rate from rest to the test periods but this was not statistically significant The heart rates of Group A patients increased more than those of Group B patients and controls but these differences did not approach significance

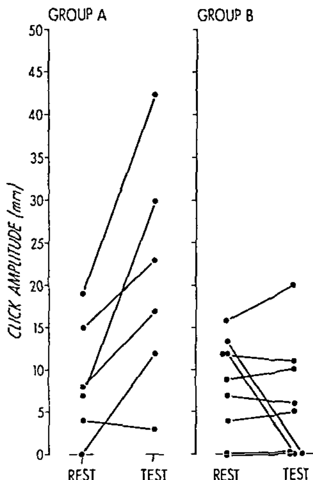


Fig 3 Changes in amplitude of the click in individual patients

Average A Trait scores were similar for all groups (± S E M) Group A = 35 5 ± 2 46 Group B = 35 3 ± 1 51 controls = 35 7 ± 7 12 The A State scores are displayed in Table III The post rest scores for patients were higher than for the controls ($p < 05$) The post rest scores for Group A and Group B were not significantly different although the group A scores were higher than those of controls ($p < 05$) whereas Group B scores were not The scores after Task I and Task II were similar for all groups

For both the patients and control subjects there was an increase in A State score from post rest to post Task II ($p < 001$) The increase for Group B was significant ($p < 001$) The higher initial anxiety score in Group A showed no significant further increase although these patients reported the highest average State anxiety after Task II

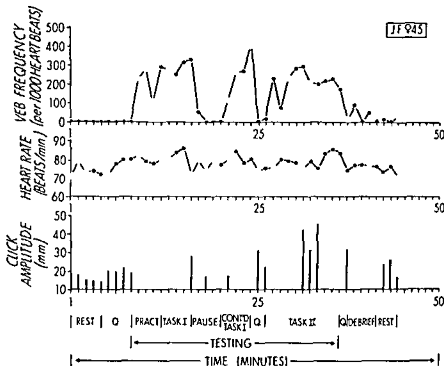


Fig 4 Response of patient J F to the psychological stress

One patient J F demonstrated a dramatic change in rhythm and click which paralleled the periods of psychological stress The details of this study are outlined in Fig 4 Of particular note is the occurrence of rhythm disturbance almost exlusively during administration of the test with a rapid return to baseline during interruptions The VEB s were multifocal and biform couplets were noted from one to seven times per minute during the tests The patient is a forty two year old female with a mid systolic click and late systolic murmur T wave inversions in Leads II III AV_F V on the resting ECG and classical MVP on echocardiogram She was the only patient in this series with the auscultatory electrocardiographic variant of the systolic click murmur syndrome At selective angiography normal coronary arteries had been demonstrated

Discussion

This study suggests that acute psychological stress exerts a significant effect on the rhythm and click in some patients with MVP It is proposed that these changes are related to the anxiety and frustration induced by the guessing tests

The click is known to change in both timing and intensity under a variety of circumstances Its presence may vary from one examination to the next [9] but this phenomenon has not been systematically evaluated In some the click is noted in only one phase of respiration either in inspiration[6] or expiration [2,4] Click changes related to posture are well known [7,10,14,19] The click occurs earlier in systole on the patient s assuming an upright posture If the click is absent in the supine position it may appear with the patient upright Amyl nitrite administration also affects the click [2,4,5,8,9,15,16,0] consistently occurring earlier with a variable effect on the amplitude Recently Towne and colleagues[11] have examined the effects of tachycardia induced by right atrial pacing The click occurred earlier in systole as pacing rates were increased Click amplitude in most subjects was unchanged or decreased as the heart rate increased but in others the click appeared only at more rapid rates (above 120/minute) The administration of pressor agents (phenylephrine and metaraminol[4]) also affects the click [4,11] with its timing generally moving later in systole and with a variable effect on amplitude The effects of psychological stress and/or anxiety on the click have not to the best of our knowledge been previously reported

In the present study the amplitude of the click

increased during psychological stress in five of 15 patients In one of the five the click also occurred earlier and in another it occurred later in systole Click amplitude decreased during stress in two patients

Patients with MVP are known to exhibit a variety of atrial and ventricular rhythm disturbances more frequently than do normals [7] Sudden death rarely occurs and may be related to ventricular tachyarrhythmias [21] Although the effects of psychological stress and/or anxiety have not been examined in MVP patients Lown and colleagues extensively studied a patient without evidence of organic heart disease in whom VEBs were provoked by psychological stress

In five of our 15 patients a new arrhythmia developed during psychological stress or an existing arrhythmia was accentuated This contrasts with the controls who exhibited no rhythm disturbances during psychological stress The arrhythmias consisted of new VEBs in three increased VEBs in one and new coronary sinus rhythm in one In one of our patients the only one with auscultatory-electrocardiographic variant a serious ventricular arrhythmia was consistently provoked by psychological stress

It is tempting to speculate that the rhythm changes and increased amplitude of the click seen in these patients are anxiety related A possibility remains that an increased amplitude of the click may be random and could reflect the natural variability of the click in this disorder However such spontaneous short term variability has not been documented Postural effects were not involved as the patients remained in one position Since five consecutive cardiac cycles were examined respiratory variations are unlikely to have played a role It is postulated that the mechanism by which anxiety alters the click and the rhythm is an increase in sympathetic nervous system tone Increased sympathetic tone with augmentation in contractility may cause an accelerated rate of ejection The click occurs during ejection at or near maximal valve prolapse and is ascribed to abrupt tensing of leaflets and chordae [2, 3] An increased rate of left ventricular ejection at the time of the leaflet prolapse might be expected to accentuate the click and there is some evidence to support this concept The click could also be affected by alterations in heart rate and blood pressure secondary to increased sympathetic tone Our subjects showed a small (and nonsignificant) increase in heart rate during the test and three of the five patients with increased click developed tachycardia (maximum being 103 beats/minute) However the evidence from pacing studies suggests that such alterations in rate should be associated with minimal if any change in the click Blood pressure was not continuously recorded during the study The risks and discomfort of intra arterial pressure measurement were not considered justifiable in this study of generally well outpatient volunteers Blood pressure measurement by cuff would have interfered with subjects concentration during testing and hence was not obtained An increase in blood pressure during the anxiety stress may also explain the finding of increased click amplitude The rhythm change in our patients may be secondary to sympathetic nervous system effect on automaticity

A particularly interesting feature of our study concerns the only patient with the auscultatory electrocardiographic variant whose behavior during psychological stress may provide some insight into a potential mechanism of sudden death in this group of patients Recent reports [28] suggest that MVP patients with the auscultatory-electrocardiographic variant may have a higher risk of sudden death The mechanism of sudden death in these patients could be related to anxiety induced arrhythmias In another report MVP patients who had experienced ventricular fibrillation were studied to ascertain factors which might increase ventricular ectopy [29] A variety of physiologic and pharmacologic interventions were employed without success but psychological stress was not used The striking response of our patient suggests that further investigation into the effects of psychological stress in a similar subset of patients may be valuable Additional work to confirm these observations and to elucidate the mechanism underlying the observed rhythm and click changes (e g administration of isoproterenol) will provide a better understanding of arrhythmias in this common syndrome The findings in the present study may explain the commonly noted variability in auscultatory findings in MVP patients If anxiety does indeed precipitate rhythm disturbances routine psychological stress testing might help to identify those in whom

certain interventions (e g behavioral modifications psychotherapy tranquilizers) could be therapeutic

Summary

Our clinical observations suggested that anxiety accentuated the click in patients with mitral valve prolapse In order to evaluate this systematically a psychological stress was administered to 30 subjects—15 patients with click murmur syndrome and 15 normal controls The phonocardiogram was recorded and the electrocardiogram were continuously monitored to assess the effects on arrhythmias

State Anxiety Inventory scores demonstrated an increase in anxiety during the psychological stress A change in rhythm during psychological stress was noted in five of the 15 patients No arrhythmias occurred in the control subjects during psychological stress ($p < .025$) Amplitude of the click increased during psychological stress in five of the 15 patients in four associated with arrhythmia

The only patient with auscultatory electrocardiographic variant developed frequent multifocal ventricular ectopics with couplets during the psychological stress

Acute psychological stress exerts important effects on the rhythm and click only in some patients with mitral valve prolapse and may provide a mechanism for intermittence of clicks and episodes of profound unexplained arrhythmias

REFERENCES

1 Ronan J A Perloff J K and Harvey W P Systolic clicks and the late systolic murmur intracardiac phonocardiographic evidence of their mitral valve origin Am Heart J 70 319 1965
2 Hancock E W and Cohn K The syndrome associated with midsystolic click and late systolic murmur Am J Med 41 183 1966
3 Behar V S Whalen R E and McIntosh H D The ballooning mitral valve in patients with the "precordial honk or whoop Am J Cardiol 20 789 1967
4 Barlow J B Bosman C K Pocock W A and Marchand P Late systolic murmur and non ejection (mid late) systolic clicks Br Heart J 30 203 1968
5 Bittar N and Sosa J The billowing mitral valve leaflet report on fourteen patients Circulation 38 763 1968
6 Shell W E Walton J A Clifford M E and Willis P W The familial occurrence of the syndrome of mid late systolic click and late systolic murmur Circulation 39 327 1969
7 Fontana M E Pence H L and Leighton R F The varying clinical spectrum of the systolic click-late systolic murmur syndrome Circulation 41 807 1970
8 Epstein E J, and Coulshed N Phonocardiogram and apexcardiogram in systolic click late systolic murmur syndrome Br Heart J 35 260 1973
9 Jeresaty R M Mitral vale prolapse-click syndrome Progr Cardiovasc Dis 15 623 1973
10 Rizzon P, Biasco G Brindicci, G and Mauro F Familial syndrome of midsystolic click and late systolic murmur Br Heart J 35 245 1973
11 LeWinter M M, Hoffman J R, Shell W E, Karliner J S and O Rourke R A Phenylephrine-induced atypical chest pain in patients with prolapsing mitral valve leaflets Am J Cardiol. 34 12, 1974
12 Barlow J B, and Pocock W A. The problem of non-ejection systolic clicks and associated mitral systolic murmurs emphasis on the billowing mitral leaflet syndrome Am Heart J 90 636 1975
13 Towne W D, Rahimtoola M B Sinno Z M Loeb H S Rosen K M, and Gunnar R M. The effects of right atrial and ventricular pacing on the auscultatory findings in patients with mitral valve prolapse Circulation 51 988 1975
14 Fontana M E Wooley C F, Leighton R F and Lewis R P Postural changes in left ventricular and mitral valvular dynamics in the systolic click late systolic murmur syndrome Circulation 51 165 1975
15 Winkle R A, Goodman D J, and Popp, R L Simultaneous echocardiographic phonocardiographic recordings at rest and during amyl nitrite administration in patients with mitral valve prolapse Circulation 51 [illegible] 1975
16 Mathey D G, Decoodt, P R Allen H N and Swart H J C The determinants of onset of mitral valve prolapse in the systolic click late systolic murmur syndrome Circulation 53 872, 1976
17 DeMaria A. N, Amsterdam E A, Vismara L [illegible] Neumann B S and Mason D T Arrhythmias in the mitral valve prolapse syndrome prevalence nature and frequency Ann Intern Med 84 656 1976
18 Spielberger C D, Gorsuch R L, and Lushene R [illegible] Manual for the State Trait Anxiety Inventory Palo Alto California 1970 Consulting Psychology Press
19 Klorman R S Plethysmographic responses to experimental stress in acute and recovered myocardial infarction patients, Doctoral Thesis, 1977 Indiana University (Unpublished)
20 Ronan J A, Perloff J K, and Harvey W P Systolic clicks and the late systolic murmur intracardiac phonocardiographic evidence of mitral valve origin Am Heart J 70 319 1965
21 Swartz, M H, Teichholz L E and Donoso E M [illegible] valve prolapse a review of associated arrhythmias Am J Med 62 377 1977
22 Lown B Temte J V, Reich P, Gaughan, C Regestein Q and Hai H Basis for recurring ventricular fibrillation in the absence of coronary heart disease and its management N Engl J Med 294 623 1976
23 Criley J M Lewis, K. B, Humphries, J O and Ross, R S Prolapse of the mitral valve clinical and cineangiocardiographic findings Br Heart J 28 488 1966
24 Mathey D G, Decoodt, P R Allen H N and Swart H J C The determinant of mitral valve prolapse in the systolic click late systolic murmur syndrome Circulation 52(Suppl. II) 209 1975
25 Campbell, R W F, Goodman M C Fiddler G Marquis R M, and Julian D G Ventricular arrhythmias in the syndrome of balloon deformity of the mitral

valve definition of a possible high risk group Br Heart J 38(10) 10.3 1976
26 Mills, B M Rose J Hollingsworth J., Amara I and Craige E Long term prognosis of mitral valve prolapse N Engl J Med 297 13 1977
27 Wei, J Y Bulkley B H Schaeffer A H and Greene H L Mitral valve prolapse syndrome and recurrent ventricular tachyarrhythmias, Ann Intern Med 89 6 19 8
28 Winkle R A Lopes M G and Popp R. L. Life threatening arrhythmias in the mitral valve prolapse syndrome Am J Med 60 961 19.6
29 Rakowski H., Waxman B M., and Wald R W Mitral valve prolapse and ventricular fibrillation Circulation (Suppl. II)52 11 93 1975

Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978 Therefore all manuscripts must be accompanied by the following written statement signed by one author The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C V Mosby Company in the event the work is published The undersigned author warrants that the article is original is not under consideration by another journal and has not been previously published I sign for and accept responsibility for releasing this material on behalf of any and all co authors Authors will be consulted when possible regarding republication of their material

Newly developed systolic murmur in patients with a transvenous pacemaker

Chiaki Shirato MD
Kyozo Ishikawa MD FACC
[illegible] Japan

[illegible] important that physicians of all disciplines [illegible]ome aware of the variations in heart sounds [illegible] murmur[illegible] that may be encountered in patients with [illegible]ndocardiac pacemakers When a newly develo[illegible] systolic murmur is observed in a patient with [illegible] tificial pacemaker serious com plication [illegible] be suspected such as rupture of the papill[illegible] muscle chordae tendineae and interventri[illegible] septum (IVS) However it should [illegible] ome in mind that such newly developed [illegible] murmurs can be observed in patients [illegible] any complications due to the artificial [illegible] ker

We rep[illegible] patients in whom a transvenous cardiac pacemaker produced a systolic musical murmur in the absence of any complications

Case reports

Case 1 A 73 year old man was admitted to Kyorin University Hospital due to a recent syn copal attack An electrocardiogram (ECG) taken on admission indicated right bundle branch block (RBBB) with left axis deviation (LAD) which was consistent with a bifascicular block Precor dial examinations on admission disclosed a normal first heart sound the second sound was physiologically split the third sound was not heard No systolic clicks were heard Prolongation of the H V interval (78 msec) was observed on the His bundle electrocardiogram Then as a safety precaution for further investigations a temporary transvenous pacemaker was inserted via the right external jugular vein and was posi tioned in what was judged to be the apex of the right ventricle (RV) A high pitched systolic mur mur suddenly appeared when the pacing was turned off The murmur persisted for several minutes after pacing off and then spontaneously disappeared (Fig 1) The same auscultatory phe nomenon was observed each time the pacemaker was switched off Switching on the pacemaker resulted in the simultaneous phonocardiographic disappearance of the systolic murmur A chest roentgenogram showed that the catheter tip was correctly positioned in the right ventricular apex There were no clinical findings suggestive of rupture of the papillary muscle chorda tendi neae ventricular perforation or twitching of the diaphragm

Case 2 A 68 year old man was referred to Kyorin University Hospital for evaluation due to shortness of breath and general fatigability On admission his pulse rate was 46/minute An ECG revealed sinus bradycardia A diagnosis of sick sinus syndrome (SSS) was established by over drive suppression tests which indicated prolonga tion of the sinus nodal recovery time (6 8 sec) A temporary transvenous pacemaker was inserted No specific murmur was auscultated when the pacing was turned off immediately after insertion of the pacemaker On the next day however a high pitched systolic murmur or so called "mu cal systolic murmur was heard at the cardiac apex when the pacing was turned off (Fig [illegible] From then on the murmur consistently appeared at each instant the pacemaker was being turned off A chest roentgenogram showed no myocardial

From the Second Departm[illegible] [illegible] Internal M[illegible] School of Medi cine Kyorin Un[illegible]ersity M[illegible]tak[illegible] [illegible] [illegible]pan
Rece[illegible]ed for publ[illegible]tion Oct 10 19[illegible]9
Accepted for public[illegible]tion Dec [illegible] 19[illegible]
Reprint requests K[illegible] I[illegible]kaw[illegible] MD [illegible] [illegible]nt of Inte[illegible] Medicine School of Medicin[illegible] K[illegible] [illegible] Mitaka-City Tokyo Japan

0002 8703/80/060722 + 0[illegible]00.[illegible]0/0 © 1980 The C V Mosby Co

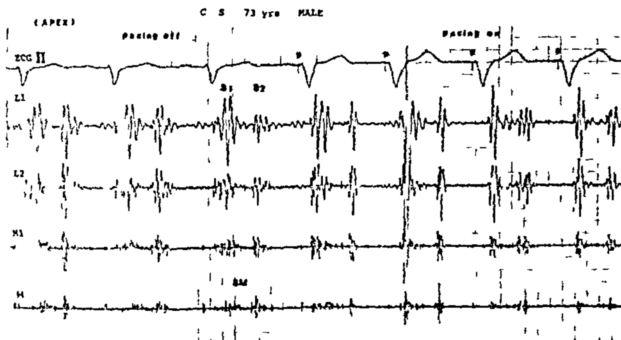


Fig 1 Phonocardiogram in Case 1 With the pacing off a diamond shaped murmur appeared in the midsystolic period and with the pacing on this murmur disappeared Abbreviations *P* pacemaker artifact S_1 The first heart sound S_2 the second heart sound *SM* systolic murmur

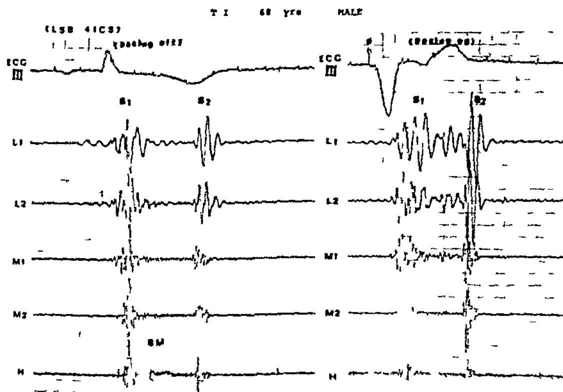


Fig 2 Phonocardiogram in Case 2 With the pacing off a high pitched systolic murmur was observed. With the pacing on the high pitched murmur was apparently diminished and the low pitched vibrations were intensified

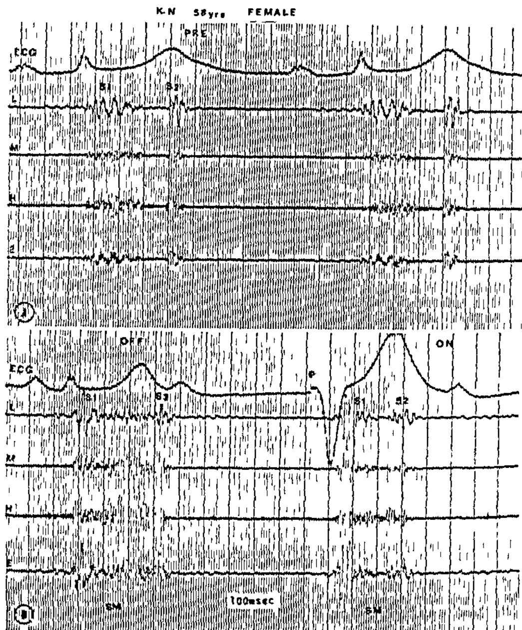


Fig 3 Phonocardiogram in Case 3 A Before pacemaker placement an early systolic murmur was observed B After pacemaker placement a high pitched murmur appeared in the mid and late systolic phases which was apparently different in quality and intensity from that observed before pacemaker placement

perforation or displacement of the pacemaker catheter Fluoroscopy revealed no unusual movement of the left hemidiaphragm Echocardiograms revealed no evidence of rupture of the chorda tendineae or papillary muscle

Case 3 A 58 year old woman was hospitalized due to dizziness and precordial pain An ECG revealed complete heart block with a ventricular rate of 42/minute A temporary transvenous pacemaker was inserted On turning the pacing off a high pitched musical systolic murmur appeared which was apparently different in intensity and quality from the murmur which had been recorded before pacemaker insertion (Fig 3) This murmur was not audible when the pacemaker was being turned on A chest x ray echocardiogram and physical examination revealed no evidence of serious complications.

Case 4 A 58 year old woman was admitted to Kyorin University due to palpitations and dizziness On admission her pulse rate was 43/minute and was irregular An ECG revealed sinus bradycardia and sinus arrhythmia Marked cardiomegaly (cardiothoracic ratio 63%) was observed on

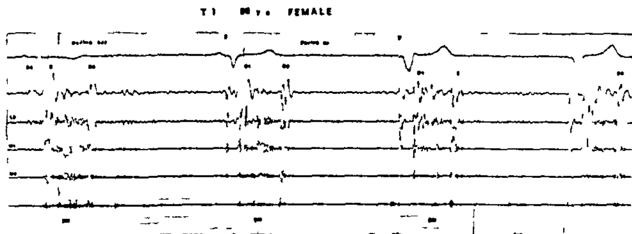


Fig 4 Phonocardiogram in Case 4 With the pacing off a high pitched systolic murmur (fishbone murmur) with its peak in the mid-systolic period was observed In the first beat after turning the pacing on no evident change was observed except for a decrease in the loudness of the murmur In the second beat and thereafter the systolic murmur was converted to a low pitched murmur and decreased in intensity

her chest x ray A grade 2/6 systolic murmur was auscultated in Erb s area Prolongation of the sinus nodal recovery time (3 4 sec) was found A temporary pacemaker was therefore inserted No specific murmur was heard when the pacing was turned off immediately after insertion of the pacemaker However on the following day a systolic musical murmur appeared which was apparently different in quality from that recorded before pacemaker insertion No physical or fluoroscopic signs of twitching diaphram or intercostal muscle were seen Furthermore there were no clinical or echocardiographic findings suggestive of serious complications such as rupture of the chorda tendineae or papillary muscle or ventricular perforation

Discussion

There have been several reports regarding the new development of heart murmur generated by insertion of transvenous catheter [2] The most common ausculatory finding in association with a transvenous pacemaker is a presystolic click (pacemaker click) which was first described by Nager and associates [3] who considered it to be of cardiac origin However subsequent studies have revealed that it is largely related to direct stimulation of the intercostal muscle or the diaphragm by a catheter electrode [6] Recently Isner and co-workers[7] suggested that the pacemaker click resulted from crisp contact of the catheter against the ventricular septum A presystolic click in a patient with an artificial pacemaker is generally considered to be an insignificant auscultatory finding although it may rarely be indicative of silent myocardial perforation or partial penetration into the right ventricular myocardium In none of our four patients however was a pacemaker click observed Bedside cardiac pacing with a transvenous catheter has become a widely used technique Yet in spite of the frequency with which this procedure is employed catheter induced cardiac murmur is apparently very unusual Why a rare auscultatory abnormality occurred in our patients remains to be established

Although the exact mechanism of production of the systolic murmur which we observed is not clearly understood we considered three possibilities as follows

1 The systolic murmur might represent tricuspid insufficiency induced by the insertion of the cardiac electrode in the RV Nachanani and associates[8] noted three patients with a systolic click and late systolic murmur described as superficial and scratchy sounding Two of the three murmurs increased in intensity with inspiration They postulated that the murmur represented tricuspid insufficiency caused by mechanical interference with tricuspid valve closure This hypothesis however seems to be less likely in our cases since the systolic murmur was of the ejection type not a regurgitant one and its intensity was not increased with inspiration Furthermore with this hypothesis it would be difficult to explain why the systolic murmur in our

cases appeared only when the cardiac pacing was being cut off

2 The systolic murmur might be attributable to endocardial friction rubs Recently Glassman and co workers[9] reported two cases having typical sounds of cardiac friction rub after placement of a temporary transvenous pacemaker They postulated that the cardiac murmur might have resulted from endocardial friction rubs due to contact of the pacing wire with the inner surface of the myocardium Like a pericardial friction rub the endocardial rub was also audible during the systolic and diastolic phases of the [illegible] cycle Although our cases showed only [illegible] murmur, the phonocardiographic pattern [illegible] systolic murmur in them revealed a rather [illegible] appearance to that of the endocardial [illegible] reported by Glass and associates[9] A [illegible] of our findings is therefore that pacing off could create a more suitable situation for the production of an endocardial friction rub

3 The systolic murmur might be generated by vibration of the pacing electrode in the RV Costeas and associates[10] reported the new development of sound and murmurs after insertion of a cardiac pacemaker which they called systolic cardiac whoop They attributed these auscultatory phenomena to movement of the pacing wire in the RV If we consider the systolic murmur in our cases on the basis of such cardiac whoop the question again arises as to why the systolic murmur occurred only when the pacing was being cut off Although an exact answer cannot be given the production of the systolic murmur in our cases could possibly have arisen from sudden pacing off altering the manner of myocardial contraction and generating a great change in blood flow in the right ventricular cavity, which could also lead to the right ventricular cavity becoming a resonant chamber

Conclusion

The finding of a pacemaker induced cardiac murmur in patients with transvenous pacemakers should be followed by a search for serious complications such as rupture of the interventricular septum chordae tendineae, or papillary muscle Whatever the genesis of this murmur may be it should be remembered, however that as the present results show a systolic murmur may be newly developed due to no apparent cause in patients with artificial pacemakers

Summary

We encountered four cases in which a transvenous cardiac pacemaker produced a systolic musical murmur in the absence of any complications This systolic murmur appeared only when the pacing was being cut off and disappeared soon after the pacing had been turned on Although the exact mechanism of production of the murmur remains uncertain several possible mechanisms for its occurrence are discussed It is apparent from this study that a systolic murmur can newly occur without any obvious cause in patients with a transvenous pacemaker

REFERENCES

1. Ishikawa K Nagoshi H Ogino T Shimada, H Hirose G., Katayama K and Hosono K. Newly developed apical systolic musical murmurs during the left heart catheterization Jap Circ J 32 1085 1968
2. Harris T and Herbert L N Study by cathode ray oscillography of some innocent and pathologic cardiac murmurs of children Am Heart J 52 881 1956
3. Nager F Buhlman A Schaub F., Schwarz, H and Senning A Auskultatorische und kardiographische Befunde bei Patienten mit implantiertem elektrischem Schrittmacher Klin Wochenschr 43 1237 1965
4. Harris A Pacemaker heart sound Br Heart J 29 [illegible] 1967
5. Pupillo G A Talley R C., and Linhart J W Pacemaker heart sound caused by diaphragmatic contractions Am Heart J 82 711 1971
6. Mandecki T Incidence and clinical significance of pacemaker sounds Cardiology 58 14 1973
7. Isner J M Horton J Ronan J A Jr Systolic click from a Swan Ganz catheter Phonoechocardiographic depiction of the underlying mechanism Am J Cardiol 43 1046 1979
8. Nachanani G H Gooch A S and Hsu I Systolic murmur induced by pacemaker catheters Arch. Intern Med 124 202 1969
9. Glassman R D Noble R J Tavel M E Storer R R and Schmidt P E Pacemaker induced endocardial friction rub Am J Cardiol 40 811 1977
10. Costeas F R Poulias, G Mastroyannis, H and Sotirakis 1 Unusual mechanical phenomena directly or indirectly related to cardiac pacing Acta Cardiol (Brux) 27 698 1972

Experimental and laboratory reports

Left ventricular function in severe pure mitral stenosis as seen at the Kenyatta National Hospital

David M Silverstein M D
David P Hansen M D *
Hillary P Ojiambo M D
Herbert E Griswold M D *
Nairobi Kenya East Africa

In Kenya as in other developing areas[1-4] it has long been the clinical impression that rheumatic heart disease follows an accelerated course with established valvular lesions presenting at a very young age This study was undertaken to evaluate this impression hemodynamically and to determine whether this rapid progression in endocardial involvement is paralleled by a similar involvement of the myocardium The model of pure mitral stenosis was used so as to obviate the possibility of left ventricular dilatation being the cause of left ventricular dysfunction

Abnormal left ventricular function in mitral stenosis has been discussed extensively in the western literature[5-11] By studying left ventricular function in this young age group and its change with advancing age we hoped to further elucidate the cause of the left ventricular dysfunction

Materials and methods

Twenty one consecutive Black African Kenyans with pure mitral stenosis underwent hemodynamic investigations at the Kenyatta National Hospital These patients were studied at an altitude of 5 400 feet and most lived at approximately this altitude Patients with coexistent aortic valve disease as determined by pullback pressure recordings and supravalvular injection or any but the most minimal mitral incompetence were excluded from this study None of the patients showed any clinical evidence of active rheumatic heart disease The age range was 6 to 50 years with a mean and standard error of 22.9 ± 9 6 years There were 15 females and six males Six patients were in atrial fibrillation and the remainder were in sinus rhythm

All patients were studied in the fasting state with meperidine and/or diazepam sedation Right and retrograde left heart catheterization were performed in all patients with additional transseptal catheterization in four Cardiac output was determined by the direct Fick principle with oxygen consumption being measured by a Collins spirometer The valve area was calculated by the Gorlin formula[12] An adequate wedge or left atrial pressure could not be obtained in six patients with severe pulmonary hypertension

After pressure recordings and cardiac output determination all patients underwent left ventricular cineangiography in the right anterior oblique projection followed by a supravalvular aortic root injection Left ventricular cineangiography was performed with the injection of 1 ml /kg of Urographin 76 at 15 ml /sec by a volume injector* and recorded on 16 mm film at

From the Departme t of Medicin Di i on of Card ology University of Nairobi Nairobi Kenya East Africa

Dr Griswold wa s pported i part by Senio Internatio l Fellowship Program F g rty International Cent N tion l Inst tutes of H lth, N 1 706 TW0085-01

Recei ed f public t n Jan. 16 19 9

Accepted f r publicat on March 19 1979

Reprint requests David M Sil erstein M D P O Box 30588 N irob Kenya Ea t Africa

Present Address Dept f Medicine Uni ersity Hosp t l San Diego Calif

Visi ing Professor Dept. of Medicin University f N irobi. Permanent Address D pt f Med cine Uni rsity f Orego Health Sciences Center P rtla d Ore

Contra IV S mens Corpo tion



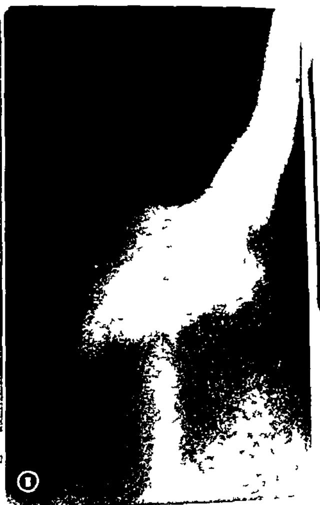


Fig 1 Illustrative cineangiogram of left ventricle *A* End-diastolic volume = 83 ml/M *B* End systolic volume = 48 ml/M

hemodynamic quantitation of the severity of mitral stenosis Combining three series where hemodynamic data is available (Table III), the mean age was 44 3 ± 12 1 compared to 22 9 ± 9 6 in our series ($p < 0.001$) As can be seen from the mitral valve indices and mean pulmonary artery pressures our patient population is comparable with regard to the severity of the disease

This study also demonstrates that the effects of the rheumatic process in mitral stenosis are not limited to the endocardium but also involve the myocardium There was significant impairment of the ejection fraction with half of the subjects having values below two standard deviations of the accepted mean This marked diminution in ejection fracton is greater than that described by most authors in western countries and is presumably indicative of a more virulent disease in our population

It however must be borne in mind that incidence studies of rheumatic mitral stenosis are not available in Kenya Patients are seldom seen in our clinic except if they present or are referred with a complaint Mass screening and routine physical examinations are still a rarity It may well be therefore that our patient population represents the severe end of a spectrum of disease This may in part explain the marked severity of both endocardial and myocardial involvement The marked pulmonary hypertension and increased pulmonary vascular resistance may also be influenced by the altitude (> 5 000 feet) at which most of our patients live and where all were studied

Left ventricular dysfunction in mitral stenosis was postulated originally on the basis of postmortem findings[illegible] and in the last decade has been confirmed in the hemodynamic laboratory by several investigators[illegible] This decrease in performance of the left ventricle is a commonly suspected

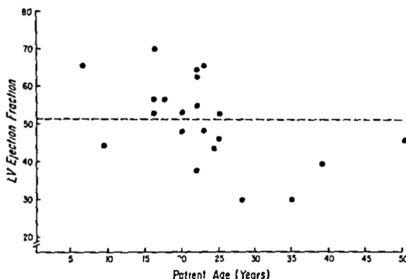


Fig 2 Left ventricular ejection fraction related to age in 21 patients with mitral stenosis The *dashed line* represents the lower limit of normal by the criteria of Kennedy et al The ejection fraction was abnormally low in 10 patients and the ejection fraction was significantly lower with increasing age

ble III

Series	*Number*	*Mean age (years)*	*Mitral valve index (cm / M)*	*Mean pulmonary artery pressure (mm Hg)*
Holtzer et al.	10	37 9	0 78	24
Curry et al	12	45 9	0 60	32
Heller et al	25	46 1	0 62	42
Cumulative	47	44 3 ± 12 1	0 64	35
Present series	21	2 9 + 9 6	0 60	50

use of poor surgical results in patients treated both commissurotomy[6] and valve replacement [2,25]

The etiology of left ventricular dysfunction in re mitral stenosis remains controversial De te the young age of the study group we do not lieve that the decreased ejection fraction bserved represented an acute carditis at the time f catheterization since patients with active eumatic fever were excluded by protocol

Furthermore if acute carditis were an impor nt factor it would be expected that the most vere impairment would be in the youngest atients i e those most likely to have active sease However, myocardial performance signif antly decreased with increasing age Out data re also inconsistent with the thesis that ecreased preload plays a significant role In fact he end-diastolic volume tended to be higher than he accepted normal values ($0.05 < p < 0.1$) This slight increase in end diastolic volume may represent compensatory dilatation

Heller and Carleton suggested that the rigid mitral complex results in decreased contractility of the posterobasal area accounting for the diminished ejection fraction Contraction plots in our patients however did not show the myocardial abnormality to be limited to this area but as others have found the decreased contractility was generalized

Another commonly suggested cause is the coexistence of ischemic heart disease Several authors have suggested that arteriosclerotic coronary artery disease is the most frequently found abnormality associated with myocardial dysfunction in valvular heart disease [27,29] The patient population in this study was far too young (22 0 ± 0 6 years with 81% under the age of 25) to implicate coronary artery disease as the cause of left ventricular dysfunction Furthermore ischemic hear

disease in Africans at the Kenyatta National Hospital is exceedingly rare

It is of interest that myocardial involvement did not parallel that of the endocardium as there was no correlation between the ejection fraction mitral valve area or any other hemodynamic index of severity However there was significant deterioration of left ventricular function with age despite there being no evidence of continued deterioration in already established severe mitral stenosis This would suggest that in our patient population myocardial deterioration is an ongoing and slower process in contrast to the early and severe endocardial involvement

Significant myocardial involvement accompanies the early severe endocardial lesion of young patients with mitral stenosis in Kenya and perhaps in other developing countries The diffuseness of the process as well as its lack of association with large and medium coronary artery disease suggests that it is a result of a diffuse myocarditis or vasculitis at the time of the initial attack of acute rheumatic fever The deterioration of left ventricular function with time we interpret as the resolution of the acute inflammatory process with development of diffuse or localized fibrosis of the myocardium and/or diffuse occlusive vasculitis both of which have been noted pathologically[30]

Summary

Twenty one consecutive Black African patients with severe pure mitral stenosis were evaluated hemodynamically It was found that advanced mitral stenosis presents itself in Kenya at a very young age (22 9 ± 9 6 years mean ± S D) with all but three patients under thirty Left ventricular angiography demonstrated significant impairment of left ventricular function with 50% of patients having abnormally low values (mean ejection fraction 0 50 ± 0 11) This diminished ejection fraction was related primarily to diffuse hypokinesia and an increased end systolic volume There was a significant deterioration of ejection fraction with increasing age which could not be correlated to increased severity of mitral stenosis or pulmonary hypertension It is proposed that the diffuseness of the myocardial involvement and its progression with age in a young population without coronary artery disease represents the resolution of the acute inflammatory process of rheumatic fever diffuse fibrosis of the myocardium and occlusive vasculitis

The authors wish to thank Ms Judy Unwin, Dr M y Warshaw and Dr S K Shah for their technical assistance in studying these patients The help of Ms C Kelso and Ms P Barkley in preparing this manuscript for publication was most appreciated Special thanks are extended to Dr Frank Kleyer for his review of this paper and for his most useful suggestions.

REFERENCES

1 Halim A M and Jacques J E Rheumatic heart disease in the Sudan Br Heart J 23 383 1961
2 Roy S B Bhatia M L Lazaro E J and Ramalingaswami V Juvenile mitral stenosis in India Lancet 2 1193 1963
3 Al Baharani I R., Thamer M A and Al Omeri M M Rheumatic heart disease in the young in Iraq Br Heart J 38 824 1976
4 Knight E O W Kamdar H H and Chukwuemeka A Juvenile mitral stenosis in Kenya East Afr Med J 50 476 1973
5 Harvey R M Ferrer M I Samet P Bader R A, Bader M E Cournand A and Richards, D W Mechanical and myocardial factors in rheumatic heart disease with mitral stenosis, Circulation 11 531 1955
6 Ferrer M I Harvey R M Cathcart P T Cournand A and Richards D W Hemodynamic studies in rheumatic heart disease Circulation 6 688 1952
7 Fleming H A and Wood P The myocardial factor in mitral valve disease Br Heart J 21 117 1959
8 Feigenbaum H Linback R F and Nasser W K Hemodynamic studies before and after instrumental mitral commissurotomy A reappraisal of pathophysiology of mitral stenosis and efficacy of mitral valvotomy Circulation 38 261 1968
9 Kennedy J W., Yarnall S R Murray J A and Figley M M Quantitative angiocardiography IV Relationships of left atrial and ventricular pressure volume in mitral valve disease Circulation 41 817 1970
10 Heller S J and Carleton R A Abnormal left ventricular contraction in patients with mitral stenosis Circulation 42 1099 1970
11 Curry G C Elliot L P and Ramsey H W Quantitative left ventricular angiocardiographic findings in mitral stenosis Am J Cardiol 29 621 1972
12 Gorlin R and Gorlin S G Hydraulic formula for calculation of area of stenotic mitral valve other cardiac valves and central circulatory shunts Am Heart J 41 1 1951
13 Dodge H T Sandler H Ballew D H and Lord, J D Jr Use of biplane angiography for the measurement of left ventricular volumes in man Am Heart J 60 762 1960
14 Greene D Carlisle R Grant C and Bunnell, I L Estimation of left ventricular volume by one plane cineangiography Circulation 35 61 1960
15 Kennedy J W Trenholme S E and Kasser I S Left ventricular volume and mass from single plane cineangiocardiograms A comparison of anteroposterior and right anterior oblique methods Am Heart J 80 343 1970
16 Kennedy J W Baxley W A Figley M M Dodge H T and Blackmon J R Quantitative angiography I The normal left ventricle in man Circulation 34 272 1966
17 Graham T P Jr Jarmakani J M and Canent R V Left heart volume estimation in infancy and childhood Circulation 43 895 1971
18 Hamilton G W Murray J A and Kennedy J W Quantitative angiocardiography in ischemic heart disease The spectrum of abnormal left ventricular function

and the role of abnormally contracting segments Circulation 45 1065 19 2.
9 Wood P An appreciation of mitral stenosis Br Med J 1 1051 1954
0 Kirch E Alterations in size and shape of individual regions of the heart in valvular disease Verh Deutsch Ges Inn Med Kong 41 374 1979
1 Grant, R. P Architectonics of the heart AM HEART J 46 405 1953
2. Kloster F E., Bristow J D., and Griswold H E. Medical problems in mitral and multiple valve replacement, Progr Cardiovasc Dis 7 504 1965
3. Peterson C R., Herr R., Crisera R V., Starr A Bristow J D and Griswold, H E The failure of hemodynamic improvement after value replacement surgery Ann Intern Med 66 1 1967
4 Litwak R S Silvay J., Gadboys H L., Lukban S B., Sakurai, H., and Castro Blanco J Factors associated with operative risk in mitral valve replacement Am J Cardiol 23 335 1969
5 Hildner F J., Linhart, J W., Samet P., Puccinini, J Marsten J L. and Greenberg J J Clinical and hemodynamic comparisons of valve replacement in patients over and under the age of sixty Ann Thorac Surg 7 438 1969
26 Holtzer J A Karliner J S O Rourke R. A and Peterson K. L Quantitative angiographic analysis of the left ventricle in patients with isolated rheumatic mitral stenosis Br Heart J 35 497 1973
27 Befeler B Kamen A R and Macleod C A Coronary artery disease and left ventricular function in mitral stenosis Chest 57 435 1970
28 Linhart J W de la Torre A Ramsey H W and Wheat M W., Jr The significance of coronary artery disease in aortic valve replacement J Thorac Cardiovasc Surg 55 811 1968
29 Linhart J W., and Wheat M W Myocardial dysfunction following aortic valve replacement J Thorac Cardiovasc. Sug 54 259 1967
30 Grismer J T Anderson R., and Weiss L Chronic occlusive rheumatic coronary vasculitis and myocardial dysfunction Am J Cardiol, 20 139 1967

Therapeutic indices for transchest defibrillator shocks: Effective, damaging, and lethal electrical doses

Charles F. Babbs, M.D., M.S., Ph.D.
Willis A. Tacker, M.D., Ph.D.
John F. VanVleet, D.V.M., Ph.D.
Joe D. Bourland, E.E., Ph.D.
Leslie A. Geddes, M.E., Ph.D.
West Lafayette, Ind.

Ventricular defibrillation by an electric shock applied across the chest is a lifesaving but not necessarily innocuous clinical procedure. Animal studies have demonstrated both morphologic damage and functional impairment of the heart following defibrillator shocks.[1-6] Indirect evidence for shock-induced myocardial damage in man includes ECG changes,[7] elevated cardiac isoenzyme levels in plasma,[8] and positive scintigrams.[9] In order to prescribe the safest and most effective electrical dose for defibrillation, knowledge of the margin of safety for defibrillator shocks is required. The classical pharmacologic measure of the margin of safety of a drug is the therapeutic index, which may be defined as the ratio of either the median toxic or the median lethal dose to the median effective dose. Because harmful effects cannot be intentionally induced in human subjects, it is necessary to consider this relationship between effective and damaging electrical doses in experimental animals. The present study establishes therapeutic indices for single damped sine wave defibrillator shocks in dogs.

From the Biomedical Engineering Center and the School of Veterinary Medicine, Purdue University, West Lafayette, Ind.

Supported by grant No. HL 1 8.5 National Heart, Lung and Blood Institute, Bethesda, Md.

Received for publication Jan. 1, 1979.

Accepted for publication Apr. 18, 1979.

Reprint requests: Dr. Charles F. Babbs, [illegible] Engineering Center, A. A. Potter Engineering Bldg., Purdue University, West Lafayette, Ind. 47907.

Methods

The experimental defibrillator. Investigations of the therapeutic and damaging effects of single damped sine wave shocks were conducted with our experimental high energy defibrillator.[1] The energy storage capacitor of this device could be varied from 0 to 100 microfarads, the series inductance could be varied from 0 to 100 millihenries, and the initial voltage of the capacitors could be varied continuously from 0 to 10,000 volts.

For the study of effective shock strengths, the operating mode of the experimental defibrillator was selected to simulate a typical clinical unit (16 or 32 microfarads, 50 or 100 millihenries, 0 to 400 joules stored energy). In this mode of operation the output pulse duration (time between pulse onset and first zero crossing of the underdamped sine wave), which is somewhat dependent upon subject resistance, averaged 5.1 msec.

For the study of toxic shock strengths, greater defibrillator capacitance (50 microfarads) charged to higher initial voltages (5,000 to 10,000 volts) was required in order to deliver sufficient energy to produce myocardial damage. *In this mode of operation shock durations averaged [illegible] msec.* In both studies the current waveforms*

*To achieve the highest electrical dose tested, corresponding roughly to the LD50, a capacitance of 100 microfarads charged to 10,000 volts was necessary in 6 of 11 animals in one group. With 100 microfarad capacitance the output waveform was an overdamped sine wave, as described in reference 10, and in this case the pulse duration was taken as the time required for the pulse to decay to 10 percent of its peak value.

0002-8703/80/060734 + 0?$00.50/0 © 1980 The C. V. Mosby Co.

were similar to those delivered by conventional damped sine wave defibrillators The delivered pulse durations were within the 2 to 10 msec range described for clinical defibrillators by Finly[11] and within the 4 to 8 msec range we calculated for typical commercially available damped sine wave defibrillators using published values for output circuit components[1] and for the range of human thoracic resistances (25 to 105 ohms) encountered clinically [13]

Animal experiments In the first study reported in detail elsewhere [1] shocks of a strength near the defibrillation threshold were tested for their efficacy in defibrillating the ventricles of 36 dogs average weight 14 ± 7* kg in which fibrillation was produced by electrical stimulation of the right ventricular endocardium Transchest ventricular defibrillation threshold was determined in each animal by repeated trials with successive shocks of diminishing peak current amplitude each shock being 10% less than that of the preceding shock The shocks were administered via 8 cm electrodes in 12 dogs weighing less than 10 kg and via 10 cm electrodes in the larger dogs The ventricles were never permitted to fibrillate for longer than 30 seconds and another fibrillation defibrillation episode was never conducted until systemic blood pressure had returned to a stable level

In the second study of damaging and lethal effects a single high intensity damped sine wave shock was given to each of 65 dogs average weight 8 ± 2* kg via 10 cm diameter transchest electrodes Details of this protocol have been reported previously [15] In brief each dog was assigned either to a control group which received no shock or to one of six experimental groups which received an unsynchronized shock of approximately 1 3 6 9 12 15 or 20 amperes peak current per kilogram body weight (90 to 4 700 joules total delivered energy) To calculate the voltage setting required to deliver the desired current the apparent chest impedance to 50 KHz non stimulating sinusoidal current was measured as described by Geddes and associates Delivered energy was calculated as previously described[1] form current and voltage waveforms registered on a storage oscilloscope Mean delivered energy doses for the groups of animals ranged from 1 to 512 joules per kilogram body weight The hearts were in normal sinus rhythm rather than fibrillation when the unsynchronized shocks were applied to ensure that any observed damage was due to the shock and not to pre existing circulatory arrest

Hearts of animals which died immediately after shock as well as hearts of animals which survived and were later killed were removed from the thorax promptly after death Gross cardiac lesions were observed carefully and were graded according to predetermined criteria [1] Entire hearts were then fixed in 10% neutral buffered formalin Blocks of myocardial tissue from 22 standardized sites were collected embedded in paraffin sectioned and stained with hematoxylin and eosin Microscopic lesions were identified and graded according to previously established criteria

Determination of efficacy damage and lethality curves The criterion for efficacy of transchest shocks was ventricular defibrillation For each of 36 dogs in the efficacy study five to 20 threshold energy values were obtained and averaged Histograms were constructed using these mean values to illustrate animal to animal variations in threshold within this population Percent successful defibrillation vs electrical dose curves were constructed for the 36 dogs according to the method of Goldstein and colleagues by integrating the threshold energy histograms Using this technique it was possible in particular to establish the 50% effective dose or ED50 for the population since one half of the dogs had defibrillation thresholds below this value and the other half of the dogs had defibrillation thresholds above this value

The criterion for toxicity of transchest shocks was any degree of morphologically detectable myocardial damage According to this criterion a heart was scored as damaged if there were any gross lesions present or if any of the 22 blocks taken for histologic study showed defibrillator induced necrosis of muscle fibers epicardial reaction or both In addition the hearts of dogs which died within 15 minutes after shock were scored as damaged although gross and microscopic lesions were often subtle at this early time after injury

The percentage of animals defibrillated damaged or killed by shock in each dose group were plotted as functions of the current or energy dose per kilogram body weight Normalization of dose

*one standard d vi tion

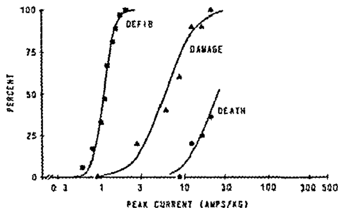


Fig 1 Current dose response curves for defibrillation morphologic damage and death The peak current has been normalized to body weight

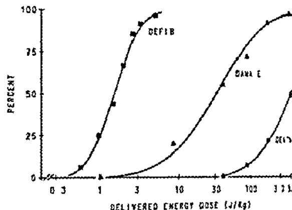


Fig 2 Energy dose response curves for defibrillation, morphologic damage and death. The delivered energy has been normalized to body weight

by body weight is classically employed in experimental pharmacology and has proved of value in earlier defibrillation studies[18] For such plots smooth curves were fitted to experimental data by probit transformation and linear regression using the method of Litchfield and Wilcoxon[19] and interpolated values were identified for the ED50 TD50 and LD50—the median effective toxic and lethal electrical doses

Results

Fig 1 shows the incidence of defibrillation morphologic damage and death as functions of delivered peak current in amperes/kg In terms of peak current the ED50 TD50 and LD50 were 1 1 5 8 and 24 amperes/kg respectively These values represent the median current doses which were capable of defibrillating damaging and killing 50% of the animals studied The corresponding therapeutic indices are TD50/ED50 = 5 for morphologically detectable damage and LD50/ED50 = 22 for death Thus it took five times as much peak current to produce detectable damage in a typical dog and 22 times as much peak current to kill a typical dog than it did to defibrillate

Fig 2 shows the incidences of defibrillation morphologic damage and death as functions of delivered energy in joules kg The ED50 TD50 and LD50 were 1 5 30 and 470 joules/kg The corresponding therapeutic indi[illegible] were TD50/ED50 = 20 for damage and [illegible] LD50 = 320 for death Hence it took 20 tim[illegible] much energy to produce detectable dam[illegible] typical dog and 320 times as much energy [illegible] typical dog than it did to defibrillate [illegible] numerical

dose range and the larger therapeutic indices may be expected when energy is used to describe shock strength because delivered energy varies as the square of the current[1]

The slopes of the curves of Figs 1 and 2 indicate considerable biologic variability among dogs in their susceptibility to defibrillation damage or death Variability in susceptibility to the harmful effects of shock was remarkable For example an electrical dose of 120 joules/kg was sufficient to kill 10% of the animals however this same dose produced no detectable damage in 12% of the animals while the remaining 78% showed varying degrees of damage Despite this biologic variability the therapeutic indices were sufficiently large so that there was no overlap between the death and the defibrillation curves and only slight overlap between the morphologic damage and the defibrillation curves The calculated curves indicate that the risk of detectable damage was 2 to 4% for 90% successful shocks and 5 to 10% for 99% successful shocks This degree of overlap between the efficacy and toxicity curves is similar regardless of whether current or energy is used to measure the electrical dose

Discussion

The studies described in the present paper indicate that therapeutic indices may be calculated for defibrillator shocks on the basis of reasonable criteria for effectiveness and "toxicity" The resultant values may be interpreted in a manner analogous to therapeutic indices of drugs Although similar studies of intentional shock overdose cannot be performed in man the therapeutic indices of various defibrillating current

waveforms can be measured in animals in order to design defibrillators with the greatest margin of safety

The relatively large therapeutic indices reported here for animals indicate a reasonable safety margin for damped sine wave defibrillator shocks Extrapolation of this conclusion to the clinical arena however must be done with caution The present studies were conducted in healthy animals with normal rather than diseased hearts Moreover in the efficacy study the time of circulatory arrest due to fibrillation was less than 30 seconds and in the damage study shocks were administered to beating hearts In general the hearts of animals in both studies were relatively well oxygenated Human hearts in clinical situations are typically diseased and may be poorly oxygenated at the time of defibrillation Under these less favorable conditions the therapeutic indices for defibrillation may be significantly different from those reported here

Nonetheless the available clinical data seem to confirm the relatively low incidence and extent of shock induced damage we have observed at therapeutic shock strengths in dogs Ehsani and colleagues and Werner and associates have shown 7 and 8% incidence respectively of indirect evidence for damage in humans after high cumulative energy doses from defibrillators Accordingly in view of both the animal and the human data available at this writing we believe that fear of inducing damage should not be a dominant factor in determining defibrillation dose Instead effectiveness should be the major criterion

Summary

Although prospective studies of defibrillator shock overdose cannot be performed in man the therapeutic indices of various defibrillating current waveforms can be measured in animals We determined the ratios TD50/ED50 and LD50/ED50 (where TD50 = median toxic or damage inducing dose ED50 = median effective or defibrillating dose and LD50 = median lethal dose) as measures of the therapeutic index for damped sine wave defibrillator shocks in dogs Death of an animal and/or any degree of cardiac damage found by gross or microscopic examination were defined as harmful effects of shock analogous to drug toxicity In terms of peak current the ED50 TD50 and LD50 were 1 1 5.8 and 24 amperes/kg the therapeutic indices were TD50/ED50 = 5 for morphologic damage and LD50/ED50 = 22 for death In terms of delivered energy the ED50 TD50 and LD50 were 1 5 30 and 470 joules/kg the therapeutic indices were TD50/ED50 = 20 for damage and LD50/ED50 = 320 for death These data indicate a reasonable margin of safety for damped sine wave defibrillator shocks in dogs and are consistent with reported incidences of suspected shock induced damage in humans

REFERENCES

1 Tedeschi, C G and White C W A morphologic study of canine hearts subjected to fibrillation electrical defibrillation and manual compression Circulation 9 916 1954

2 Dahl C F Ewy G A and Warner E D Myocardial necrosis from direct current countershock. Effect of paddle electrode size and time interval between discharges Circulation 50 956 1974

3 Warner E D Dahl C and Ewy G A Myocardial injury from transthoracic defibrillator countershock Arch Pathol. 99 55 1975

4 Tacker W A Davis, J S Lie J T Titus J L., and Geddes, L. A. Cardiac damage produced by transchest damped sine wave shocks Med Instrum. 12 27 1978

5 VanVleet J F Tacker W A., Geddes, L. A., and Ferrans, V J Acute cardiac damage in dogs given multiple transthoracic shocks with a trapezoidal waveform d fibrillator Am J Vet. Res. 38 617 1977

6 Davis J S Lie J T Bentinck, D C Titus J L., and Geddes, L. A Cardiac damage due to electric current and energy Light microscopic and ultrastructural observations of acute and delayed myocardial cellular injuries, Proceedings Cardiac Defibrillation Conference Purdue University W Lafayette Indiana 1975

7 Resnekov L High-energy electrical current and myocardial damage Med Instrum 12 24 1978

8 Ehsani, A Ewy G A., and Sobel B E Effects of electrical countershock on serum creatinine phosphokinase (CPK) isoenzyme activity Am J Cardiol 37 12 1976

9 DiCola V C Friedman G S Downing S E., and Zaret, B L. Myocardial uptake of technetium 99m stannous pyrophosphate following direct current transthoracic countershock, Circulation 54 980 1976

10 Geddes, L. A., Bourland, J D Coulter T W Canntrell, G Moore A G Vasku J Cabler P., and Tacker W A A megawatt defibrillator for transchest defibrillation of heavy subjects Med. Biol Eng 11 747 1973

11 Finlay J B Choosing and maintaining D C defibrillators, J Cardiovasc Tech. 20 99 1978

12 Babbs C F and Whistler S J Evaluation of the operating internal resistance inductance and capacitance of intact damped sine wave defibrillators Med. Instrum. 12 34 1978

13 Machin J W., Thoracic impedance of human subjects Med. Biol. Eng. Comput. 16 169 1978

14 Babbs, C F., Whistler S J., and Yim G K W Temporal stability and precision of ventricular defibrillation threshold data, Am J Physiol. 4 H553 1978

15 VanVleet J F Tacker W A Geddes, L. A., and Ferrans, V J Sequential morphologic alterations induced by single transthoracic damped sinusoidal wave

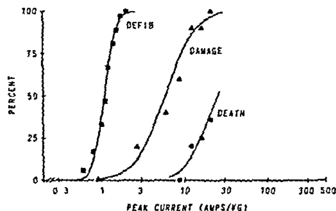


Fig 1 Current dose response curves for defibrillation morphologic damage and death The peak current has been normalized to body weight.

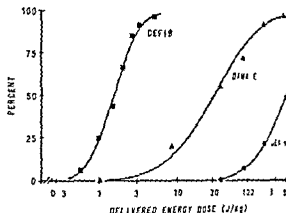


Fig 2 Energy dose response curves for defibrillation, morphologic damage and death. The delivered energy has been normalized to body weight

by body weight is classically employed in experimental pharmacology and has proved of value in earlier defibrillation studies[18] For such plots smooth curves were fitted to experimental data by probit transformation and linear regression using the method of Litchfield and Wilcoxon[19] and interpolated values were identified for the ED50 TD50 and LD50—the median effective toxic and lethal electrical doses

Results

Fig 1 shows the incidence of defibrillation morphologic damage and death as functions of delivered peak current in amperes/kg In terms of peak current the ED50 TD50 and LD50 were 1 1 5 8 and 24 amperes/kg respectively These values represent the median current doses which were capable of defibrillating damaging and killing 50% of the animals studied The corresponding therapeutic indices are TD50/ED50 = 5 for morphologically detectable damage and LD50/ED50 = 22 for death Thus it took five times as much peak current to produce detectable damage in a typical dog and 22 times as much peak current to kill a typical dog than it did to defibrillate

Fig 2 shows the incidences of defibrillation morphologic damage and death as functions of delivered energy in joules/kg The ED50 TD50 and LD50 were 1 5 30 and 470 joules/kg The corresponding therapeutic indices were TD50/ED50 = 20 for damage and LD50 = 320 for death Hence it took 20 times as much energy to produce detectable damage in a typical dog and 320 times as much energy to kill a typical dog than it did to defibrillate The numerical

dose range and the larger therapeutic indices may be expected when energy is used to describe shock strength because delivered energy varies as the square of the current[17]

The slopes of the curves of Figs 1 and 2 indicate considerable biologic variability among dogs in their susceptibility to defibrillation damage or death Variability in susceptibility to the harmful effects of shock was remarkable For example an electrical dose of 120 joules/kg was sufficient to kill 10% of the animals however this same dose produced no detectable damage in 12% of the animals while the remaining 78% showed varying degrees of damage Despite this biologic variability the therapeutic indices were sufficiently large so that there was no overlap between the death and the defibrillation curves and only slight overlap between the morphologic damage and the defibrillation curves The calculated curves indicate that the risk of detectable damage was 0 to 4% for 90% successful shocks and 5 to 10% for 99% successful shocks This degree of overlap between the efficacy and toxicity curves is similar regardless of whether current or energy is used to measure the electrical dose

Discussion

The studies described in the present paper indicate that therapeutic indices may be calculated for defibrillator shocks on the basis of reasonable criteria for effectiveness and toxicity The resultant values may be interpreted in a manner analogous to therapeutic indices of drugs Although similar, studies of intentional shock overdose cannot be performed in man the therapeutic indices of various defibrillating current

The influence of early repolarization variant on the exercise electrocardiogram a correlation with coronary arteriograms

Benjamin N Alimurung M D
Charles A Gilbert M D F A C C
Joel M Felner M D F A C C
Robert C Schlant M D F A C C
Atlanta Ga

Current criteria for positive and negative tread mill stress tests are based largely on exercise induced S T segment changes in persons with a normal electrocardiogram at rest A distinctive pattern of S T segment elevation in the resting electrocardiogram of apparently healthy adult subjects referred to in a variety of terms includ ing unusual RT segment deviation juvenile pattern of adult Negro males premature repo larization [3] normal RS T elevation variant and early repolarization syndrome has been described Previous investigators have stated that persons with S T segment elevation of the early repolarization variant (ERV) have S T segments return to the isoelectric baseline with physical exercise The authors concluded that such response to exercise favors a diagnosis of normal variant but no correlations with coronary arteriograms were performed The purpose of our study is (1) to provide coronary angiography data and treadmill exercise testing correlations in this syndrome of ERV and (2) to characterize the influence of ERV on the exercise electrocardio gram in a subset of patients with chest pain of possible cardiac origin

F om th Departm nt of Med cine Divis on f C rd ol gy Emory University School of Med cine and Grady M morial Hosp tal Atlan ta

Recei ed for publicat n Feb 28 1979

Accepted fo publ cation Apr 17 1979

Reprint requests Joel M F lner M D 69 B tler St S E Atl ta Ga 30303

Dr Feln r is prese tly a T aching Schol r f th Am rican Heart Association

Materials and methods

During the 90 month period between January 1968 and June 1976 264 patients were referred to the Cardiac Function Laboratory at Grady Memorial Hospital Atlanta Georgia for evalua tion of a variety of cardiovascular related prob lems All patients underwent both graded tread mill exercise testing and cardiac catheterization studies including selective coronary cineangiogra phy This subgroup of 264 patients was actually drawn from a much larger population of cardiac patients who did not have both procedures per formed Of these 264 patients were 16 patients seen specifically for evaluation of chest pain syndromes of possible cardiac origin who had resting scalar electrocardiograms characteristic of early repolarization [6 8 9]

The 16 patients consisted of nine black males and seven black females (Table I) Their ages ranged from 27 to 59 years (mean, 42 4 years)

Electrocardiograms All patients included in this study had a minimum S T segment elevation of 0 5 mm above the isoelectric line in at least two standard limb or precordial leads and in addition in at least one of the four monitored leads at rest (Fig 1) Frank orthogonal X Y and Z leads and a bipolar CM lead The magnitude of S T segment displacement was measured by two of the investi gators (B N A and C A G) from the lowest point of the S T segment at least 0 08 sec after the RS T junction (J point) to a baseline con structed by aligning a straight line with succes sive T P segments The amount of displacement

0002 8 03/80/060739 + 07$00 0/0 © 1980 The C V Mosby Co

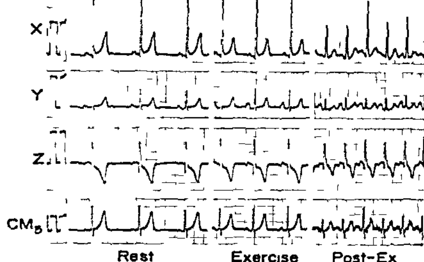


Fig 1A This figure shows the typical response of early repolarization variant (ERV) seen in the *left panel (Rest)* to be normalized by exercise in one patient The *middle panel* shows an early stage of exercise *(Exercise)* while the *right panel* (Post Ex) is immediately after exercise has stopped The ST segment has returned to the isoelectric baseline in the post-ex recording This is not an abnormal or "ischemic" response to exercise and the coronary angiograms were normal

Table I Clinical profile

Case no	*Age*	*Sex*	*Major cardiac problems*	*Medications*
1	27	F	Chest pain rheumatic heart disease with AR and MR	Digitalis sulfadiazine
2	33	M	Chest pain	None
3	34	M	Chest pain essential hypertension	None
4	37	F	Chest pain rheumatic heart disease with AR MS and MR	Sulfadiazine
5	37	F	Chest pain	Nitroglycerin
6	40	M	Chest pain AR and AS (unknown etiology)	Digitalis thiazide
7	42	F	Chest pain essential hypertension	Nitroglycerin thiazide methyldopa
8	43	F	Chest pain AR (unknown etiology) essential hypertension	Digitalis thiazide
9	43	M	Chest pain suspected MI without objective data	Nitroglycerin thiazide
10	49	M	Chest pain essential hypertension	Methyldopa propranolol nitroglycerin thiazide digitalis
11	51	F	Chest pain essential hypertension	Nitroglycerin propranolol, thiazide
12	54	M	Stable angina pectoris essential hypertension	Nitroglycerin thiazide propranolol hydralazine
13	55	M	Chest pain hypercholesterolemia suspected MI without objective data	Nitroglycerin
14	57	M	Stable angina pectoris essential hypertension suspected MI without objective data	Thiazide propranolol nitroglycerin digitalis
15	58	M	Chest pain	Nitroglycerin
16	59	F	Chest pain	Nitroglycerin digitalis

Abbreviations AR = aortic regurgitation AS = aortic stenosis MS = mitral stenosis MR = mitral regurgitation MI = myocardial infarction

was averaged from five successive complexes on the electrocardiogram The same technique of measurement was utilized in quantitating ST segment changes during exercise ST segment elevation was determined to the nearest 0 5 mm

Exercise protocol A modified [illegible] stage Bruce exercise protocol was used utilizing a standard commercially available motor-driven belt treadmill with variable speed and variable elevation capabilities All patients had continuous electrocardiographic monitoring through a Frank orthogonal X Y Z and a CM bipolar lead system

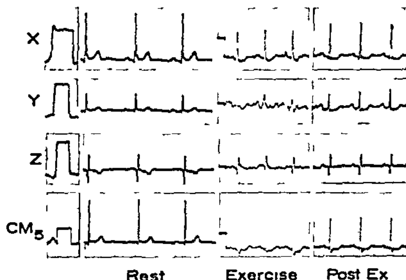


Fig 1B Another patient s record is seen with progression of the resting ERV *(left panel)* so that the ST segment is below the isoelectric baseline during exercise *(middle panel Exercise)* In the *right panel (Post Ex)* taken 1 to 2 minutes after exercise the ST segments are seen to be 1 mm below the baseline especially in Lead CM This abnormal or "ischemic response occurred in the patient with two-vessel coronary atherosclerotic disease by coronary angiography (patient No 12)

Each patient became familiar with the exercise procedure by a warm up period (Stage 0) that consisted of walking on the treadmill at a very low energy level (1 0 m p h and 5% grade) for three minutes Stage 0 was not added to the total duration of exercise score referred to as treadmill exercise duration score (TDS)[10] Each patient then walked for three minutes at each successive stage Heart rates and blood pressures were recorded at rest before the test during each exercise stage and several times during recovery from exercise Electrocardiograms of the monitored lead system were also recorded before and during the test and during recovery from exercise Patient observation was extended for eight minutes following termination of exercise All patient symptoms were carefully noted The exercise endpoints from the patients were any of the following (1) chest pain judged by the physician observer as consistent with myocardial ischemic pain (2) excessive fatigue (3) significant decrease in systolic blood pressure sustained during the successive blood pressure determinations (4) marked S T segment changes or (5) significant arrhythmia judged as dangerous for the patient All exercise blood pressure determinations were obtained from a standard sphygmomanometer by the same physician observer during each individual exercise test

Cardiac catheterization and coronary cineangiography All patients underwent left heart catheterization and standard selective coronary cineangiography using a percutaneous transfemoral approach Technically high quality left ventriculograms and coronary cineangiograms were obtained with angiographic dye injection The degree of coronary artery obstruction was expressed as the percentage decrease in artery diameter In addition the severity of cardiac valvular lesions was assessed in four patients

Results

All 16 patients presented with chest pain of possible cardiac origin (Table I) The chest discomfort was defined as angina pectoris in two of the patients who described the discomfort as retrosternal provoked by effort lasting less than 15 to 20 minutes and subsiding in 3 to 5 minutes with rest or the administration of sublingual nitroglycerin One patient with angina pectoris and two additional patients had been hospitalized for suspected myocardial infarction without diagnostic electrocardiographic and/or enzyme changes of myocardial necrosis No patient had physical findings of a ventricular aneurysm

Seven of the patients six requiring antihyper tensive drugs had well controlled essential arterial hypertension Four patients had valvular lesions involving the mitral and/or the aortic valve Because the patients were not entered

Table II

Case no	RS T segment displacement resting ECG															
	I	II	III	aV_R	aV_L	aV_F	V	V	V	V	V	V_6	X	Y	Z	CM
1	+	+			+						+	+	+	+		++
2	+				+			+	+	+			+		+	+
3	++	+			+			+	+	+++	+++	++	+	++	++	+
4		+	+			+					++	++	+	+	++	+
5	+						+	++	+	+	+	+	+		+	
6									+	++					++	++
7	+	+			+			+	++	++	+	+	++			
8	++				+			+	+	+	+		++		+	+
9			+			+			++	+	+	+	++	+	+	++
10								+	+	+			+	+	+	+
11								++	+	+			+		+	
12	+	+			+					+	+	+	+			+
13							++	+++	++	+	+	+	+		++	+
14								+	+	+					+	
15	+				+			++	++	++	+	+	+			
16							+	+	+						++	

Symbol and abbreviations ECG = electrocardiogram + = 0.5 mm but less than 1 0 mm elevation ++ = 1 2 mm elevation +++ = greater than 0 mm elevation

Table III Summary of responses during TMET

Case no	Peak HR	Peak SBP	DP*	Chest pain	S T segment changes		TDS (minutes)
					Isoelectric	at HR	
1	00	150	30 00	No	Yes	167	6 1
2	177	200	35 40	No	Yes	136	10 1
3	180	220	39 60	Yes	Yes	160	10 3
4	150	145	21 75	No	Yes	150	4 0
5	187	160	29 92	No	Yes	145	8 3
6	150	160	24 00	No	Yes	150	9 0
7	170	200	34 00	No	Yes	175	9 0
8	177	188	33 28	No	Yes	145	4 0
9	136	160	21 76	Yes	Yes	120	8 0
10	167	170	28 39	Yes	No (1.5 mm depression)	158	9 4
11	143	220	31 46	No	Yes	100	4 4
12	115	160	18 40	Yes	No (1 0 mm depression)	115	4 9
13	136	155	21 08	No	Yes	136	8 1
14	107	125	13.38	Yes	No (1 0 mm depression)	100	6 0
15	150	200	30 00	No	Yes	125	5 4
16	150	180	27 00	No	Yes	150	3.8

Abbreviations HR = heart rate SBP = systolic blood pressure DP = double product (peak HR × peak SBP) TDS = treadmill duration score TMET = treadmill exercise test
* = divided by 1000

the study in a prospective fashion and because most of the group had other cardiac disorders requiring therapy 14 of the patients were receiving various cardiac medications at the time of exercise testing These included a thiazide diuretic in nine digoxin in six and propranolol in four

S T segment elevation resting electrocardiogram S T segment elevation was present in 13

patients in Leads V_3 V and in the Frank ortho-
gonal Lead X in 12 patients in the Frank ortho-
gonal Lead Z in 11 patients in Lead V and in 10
patients in Lead V_3 (Table II) Among the limb
leads S T segment elevation was most prevalent
in Lead I (eight patients) No patient had S T
segment elevation in lead aV_R The mean spatial
S T vector was therefore directed to the left
inferiorly and anteriorly in the majority of the

Table IV Cardiac catheterization data

Case no	*LV contractility*	*Coronary arteriography*	*LVEDP (mm Hg)*		*Ej Fx %*	*Valvular lesions*
			Pre-angio	*Post angio*		
1	Moderate diffuse hypokinesis	Normal	12	18	51	AR (moderate) MR (trivial)
2	Normal	Normal	10	12	57	None
3	Normal	Normal	12	4	91	None
4	Normal	Normal	16	16	72	AR (moderate) MS (moderate) MR (mild)
5	Normal	Normal	9	13	70	None
6	Mild diffuse hypokinesis	Normal	8	N D	60	AR (severe) MS (mild)
7	Normal	Normal	8	12	6[illegible]	None
8	Normal	Normal	5	5	88	AR (mild to moderate)
9	Normal	Normal	6	N D	60	None
10	Normal	Normal	[illegible]	24	61	None
11	Mild diffuse hypokinesis	Normal	12	17	45 (post angio = 58)	None
12	Normal	75% proximal ALOM 75% proximal LAD	13	2[illegible]	79 (post angio = 82)	None
13	Normal	Normal	16	10	75	None
14	Normal	75% proximal LAD	6	N D	78	None
15	Mild diffuse hypokinesis	Normal	12	16	N D	None
16	Normal	Normal	10	28	76	None

Abbreviations LV = left ventricle LVEDP = left ventricular end-diastolic pressure Ej Fx = ejection fraction LAD = left anterior descending ALOM = anterolateral obtuse marginal N D = no data A R = aortic regurgitation M S = mitral stenosis M R = mitral regurgitation

patients Six patients (38% of the cases) had no S T segment elevation in the limb leads but all patients with S T segment elevation in the limb leads also had S T segment displacement in the precordial leads

There was no relationship discernible between the patient s major and cardiovascular disorders edications and the degree and distribution on T segment elevation in his resting electrocar ograms

Correlation of treadmill exercise responses ith cardiac catheterization and coronary angio raphic data A summary of the pertinent tread ill exercise data is presented in Table III Six of he patients attained a treadmill exercise dura ion score (TDS) of 85% or greater of predicted verage TDS for normal sedentary subjects four chieved a TDS of 60% to 84% and the remaining ix of the 16 patients had a TDS of 43% to 59% alues for average exercise heart rates for age nd sex matched sedentary normal subjects were rawn from the author s (C A G) own exercise aboratory data[1]

None of the 16 patients had his resting S T egment elevation increase with exercise In 13 atients (81%) the elevated S T segments returned to the isoelectric baseline (normalized) during exercise with heart rates between 100 and 167 beats per minute (mean 139 beats per minute) All 13 of these patients had normal coronary arteriograms (Table IV) and none had angiographic evidence of a left ventricular aneurysm Three of these 13 patients had mild to moderate diffuse left ventricular hypokinesis but with normal coronary arteries (Table IV) In two patients (Nos 1 and 6) the left ventricular dysfunction was probably due to moderate to severe chronic aortic regurgitation whereas in the third (No 15) it was unexplained The remaining three (Nos 10 12 and 14) of the 16 patients developed significant S T segment depression (1 0 to 1 5 mm) at an exercise heart rate of 158 115 and 100 beats per minute respectively Of these three patients two (Nos 12 and 14) had significant coronary atherosclerotic occlusive lesions (Table IV) whereas the third (No 10) had normal coronary arteries and normal left ventricular contractility but moderately increased left ventricular end diastolic pressures This latter patient had hypertensive cardiovascular disease and a history of chronic alcohol abuse

Chest pain experienced during exercise did not

permit separation of patients with significant coronary atherosclerotic disease from the rest of the study group with normal coronary anatomy (Tables III and IV)

Rare premature supraventricular and unifocal premature ventricular complexes not previously present in the resting electrocardiograms were observed during exercise in patients No 1 and No 10 and in patient No 13 respectively No other arrhythmias were noted during or following exercise in the 13 other patients in our study

Discussion

Typically the S T segment of the early repolarization variant (ERV)[4,5] is characterized by an upward concave elevation of the RS T segment that arises from the descending limb of the R wave in a smooth curve without forming a sharp angle with that R wave (Fig 1) The S T segment merges with the ascending limb of a usually tall positive and peaked T wave In addition a definite notch or slur on the downstroke of the R wave and/or a distinct J wave are frequently present

In our patients and those reported by others[4,5] the characteristic S T segment elevation was most prominent and most frequently observed in the standard limb Lead I and in the midprecordial Leads (V and V_4) and no patient had the S T elevation limited to limb leads alone In the majority of instances S T displacement did not exceed 2 mm However Goldman[6] reported 23 predominently young healthy adults whose electrocardiograms had shown S T elevations of 2 to 4 mm in the mid and left precordial Leads (V through V)

Although the ERV has been encountered in patients with a variety of cardiac disorders[1,5] including rheumatic valvular and coronary atherosclerotic heart disease this electrocardiographic finding is not an objective marker of cardiac disease The ERV is seen in approximately 2 5%[1] to 6 1% of apparently healthy adults Although it has been observed in either Black or Caucasian individuals some studies report a higher prevalence of the ERV in young adult Black males

The precise electrophysiologic genesis of the S T segment elevation is unknown Several possible explanations previously [illegible] include (1) hypervagotonia (2) [illegible] and early repolarization in the [illegible] ardium occurring before depolarization [illegible] whole myocardium[4,11]

The benign nature of the ERV has bee[n] established by longitudinal follow up[4,11] [of] individuals with this electrocardiographic [pattern] In a recent review of the electrocardiogram[s of] patients with the ERV syndrome Kamba[ra and] Phillips[5] found persistence of this patte[rn for] many years and a general tendency to dec[rease] S T segment displacement with increased a[ge. In] 26% of their 65 patients the S T elevation [disap]peared in at least one follow up electroc[ardio]gram, while in the 48 other patients [the] elevation was discernible in every recording [Fur]thermore, the degree of S T displacement [varied] greatly from one electrocardiogram to anot[her in] the individual patient Others[1,4,7] have re[ported] that individuals with the ERV with S T se[gment] elevation at rest have S T segments return[ing to the] isoelectric baseline (normalize) with ph[ysical] exercise, and concluded that such response [favors] a diagnosis of normal variant and no hear[t dis]ease—but no correlations with coronary ar[terio]grams were performed

Our study provides correlates between [the] responses to treadmill exercise testing and [coro]nary cineangiography in patients with ER[V and] verifies the benign nature of this finding I[n a] subset of patients with chest pain of pos[sible] myocardial origin and S T segment eleva[tion] suggestive of ERV in the resting electrocar[dio]gram all except one patient (No 10 with nor[mal] coronary arteriograms) had the S T segm[ent] return to the isoelectric baseline with tread[mill] exercise Thus patient (No 10) without evide[nce] of coronary atherosclerotic disease but with m[od]erate left ventricular dysfunction of unkno[wn] cause developed significant S T depression ([ ] mm below isoelectric baseline) during treadm[ill] exercise Two patients (Nos 12 and 14) w[ith] significant coronary atherosclerotic disease dev[el]oped similar ischemic S T segment depress[ion] with exercise Thus while ERV at rest may [be] normalized by graded physical exercise in t[he] absence of significant coronary atheroscleros[is] the presence of ERV does not prevent the us[ual] electrocardiographic manifestations of exercise induced myocardial ischemia

The influence of propranolol and digitalis o[n] the response of the ERV to physical exercise [is] unknown Several studies[1,2] report that pro[pranolol may prevent the appearance of ischemic electrocardiographic changes even when exercise is continued to the onset of myocardial ischemic pain and may change a positive exercise test to a

negative result These observations however did not involve patients with the ERV The influence of propranolol on the response of the ERV to exercise stress testing remains speculative Interestingly in our series only the two patients with significant coronary atherosclerotic disease and positive ischemic S T segment depression provoked with exercise were receiving propranolol at the time of treadmill testing Digitalis on the other hand can elicit a false positive ischemic exercise electrocardiographic response in persons without myocardial ischemia [?] In our patients with the ERV, however digitalis did not appear to produce false positive ischemic S T segment changes during exercise

Summary

Sixteen adult patients with S T segment elevation in their resting electrocardiograms characteristic of early repolarization variant (ERV) and chest pain syndromes of possible myocardial ischemia were evaluated with both treadmill exercise electrocardiography and coronary arteriography Of 14 patients with normal coronary arteriograms 13 had their resting S T elevation return (normalize) to the isoelectric baseline with physical exercise while one patient with normal arteriograms and normal left ventricular contractility but moderately elevated left ventricular end diastolic pressure of unknown etiology developed significant S T depression with exercise Two patients with significant coronary atherosclerotic occlusive lesions developed ischemic S T depression during treadmill testing Symptoms developed during treadmill exercise did not distinguish patients with coronary artery disease from those without Thus while ERV at rest may be normalized by graded physical exercise in the absence of significant coronary atherosclerosis, the presence of ERV does not prevent the usual electrocardiographic manifestations of exercise induced myocardial ischemia

We thank Cheryl Flowers and Charline Hutton for their excellent secretarial assistance in the preparation of the manuscript

REFERENCES

1 Chelton L G and Burchel, H B Unusual RT segment deviation in electrocardiograms of normal persons Am J Med Sci 230 54 1955
2 Wasserburger R H Observations on the juvenile pattern of adult Negro males Am J Med 18 4?8 1955
3 Gottschalk C W and Craige E A comparison of the precordial S-T and T waves in the electrocardiograms of 600 healthy young Negro and white adults, South Med J 49 453 1956
4 Wasserburger R. M., Alt W J., and Lloyd C The normal RS-T segment elevation variant Am J Cardiol 8 184 1961
5 Kambara H and Phillips J Long term evaluation of early repolarization syndrome (normal variant RS-T segment elevation) Am J Cardiol. 38 157 1976.
6 Goldman M J RS-T segment elevation in mid and left precordial leads as a normal variant Am Heart J 46 817 1953
7 Surawicz B and Saito S Exercise testing for detection of myocardial ischemia in patients with abnormal electrocardiograms at rest Am J Cardiol. 41 943 1978
8 Hiss R G Lamb L E and Allen M F Electrocardiographic findings in 67 375 asymptomatic subjects X Normal values Am J Cardiol 6 200 1960
9 Goldman M J Normal variants in the electrocardiogram leading to cardiac invalidism Am Heart J 59 71 1960
10 Gilbert, CA Exercise testing of cardiac function *in* The heart 4th ed., Hurst J W., Logue R B Schlant R C and Wenger N K., eds New York 1978 McGraw Hill Book Company p 516-520
11 Wood J D and Laurie W The electrocardiogram of the South African Bantu Circulation 19 2?1 1959
12 Greene C E and Kelly J J Electrocardiogram of the healthy adult Negro Circultion 20 906 1959
13 *Thomas, J Harris, E and Lassiter G Observation on* the T wave and S-T segment chan es in the precordial electrocardiogram of 3?0 young Negro adults Am J Cardiol 5 468 1960
14 Parisi A F Beckmann C H and Lancaster M C The spectrum of ST segment elevation in the electrocardiograms of healthy adult men J Electrocardiology 4 137 1971
15 Fenichel N N A long term study of concave RS-T elevation—a normal variant of the electrocardiogram Angiology 13 360 1962
16 Grusin H Preculiarities of the African s electrocardiogram and the chan es observed in serial studies, Circulation 9 860 1954
17 Grant R P Estes E H and Doyle J T Spatial vector electrocardiography The clinical characteristic of S-T and T vectors Circulation 3 182 1951
18 Sommers, K and Rankin A M The electrocardiogram in healthy East African (Bantu and Nilotic) men Br Heart J 24 54? 1962.
19 Prichard B N C and Gilliam P M S Assessment of propranolol in angina pectoris. Clinical dose response curve and effect on electrocardiogram at rest and on exercise Br Heart J 33 473 1969
20 Gianelly R E., Treister B L. and Harrison D C The effect of propranolol on exercise induced ischemic S-T segment depression Am J Cardiol 24 161 1969
21 McHenry P L. and Morris, S M Exercise electrocardiography—current state of the art *in* Advances in electrocardiography Schlant R C and Hurst J W., eds., New York 1976 Grune & Stratton Inc., p 265 304
22 Kawai C and Hultgren H N The effect of digitalis upon the exercise electrocardiogram Am Heart J 68 409 1964
23 Hirsch E. Z. The effects of digoxin on the electrocardiogram after strenous exercise in normal men Am. Heart J 70 196 1965

Bleeding during acetylsalicylic acid and anticoagulant therapy in patients with reduced platelet reactivity after aortic valve replacement

Jon Dale M D
Eric Myhre M D
Dieter Loew M D
Oslo Norway

The antithrombotic effects of drugs that modify platelet functions have been evaluated in several clinical trials[1] Such agents may be particularly useful in conditions related to arterial thrombosis because platelets play a dominant role in the formation of the thrombi.[11] Platelet adhesion release and aggregation are important steps in the thrombotic process[1] Several drugs inhibit the platelet release reaction and thereby the subsequent irreversible aggregation[12] Most important are acetylsalicylic acid (ASA) indomethacin sulfinpyrazone and butazolidin while dipyridamole may reduce platelet aggregation through other mechanisms[13] ASA is most extensively used and the results from several studies indicate a preventive effect on arterial thrombus formation

Anticoagulant in adequate doses effectively prevents venous thromboembolism because plasma coagulation is the predominant mechanism in this type of thrombosis Low dose heparin administration has recently been introduced as an alternative treatment in this condition[1] Anticoagulant drugs are also widely used in the prevention of arterial thrombosis particularly after prosthetic valve implantation and are employed by several centers in coronary heart disease The effect is limited however and further research is needed to find a therapy that effectively inhibits arterial thrombus formation The combination of drugs that modify platelet function and anticoagulants may prove useful since it attacks more than one step in the thrombotic process[9] A combination of anticoagulants with dipyridamole[3] and later with ASA[9, 10] gave an antithrombotic effect superior to anticoagulants alone in patients with prosthetic heart valves Others have combined two drugs that affect platelet function[17]

All agents that inhibit thrombus formation are potential inducers of bleeding since the mechanisms responsible for stopping hemorrhage are the same that form thrombi when stimulated pathologically[11] Combined antithrombotic therapy might be particularly dangerous since it affects more than one part of the hemostatic mechanism Therefore the tendency of bleeding that a therapy may induce should always be evaluated along with its antithrombotic effects

Patients with prosthetic heart valves are particularly useful for studies on prevention of arterial thromboembolism because such complications are frequent and quite well defined[1] In such patients however the platelet adhesiveness is reduced[18] the bleeding time is prolonged and platelet survival is shortened[1, 21] most probably because of trauma inflicted by the prosthetic valves[1, 22] This reduced platelet reactivity might in itself predispose to bleeding

Patients with aortic ball valve prostheses have participated in a randomized clinical trial and have received either anticoagulants alone or com

From Medical Department B and Institute ... Research Rikshospitalet University Hospital Oslo Norway

Received for publication M
Accepted for publication J

Reprint requests Dr J D Med ... Rikshospitalet Oslo 1 Norway

bined with ASA[9] In the present study the bleeding complications are analyzed in relation to platelet function intensity of anticoagulant treatment and administration of ASA

Materials and methods

Patient material Included in the study were 148 patients who had received a Starr Edwards aortic ball valve more than two years previously and who were willing to participate Two types of the valve had been used series 1200 with silicone rubber ball and metal cage and series 2300 with hollow Stellite ball and cloth covered cage Twenty-one patients had been excluded either because they were older than 70 years had suffered gastrointestinal or other types of bleeding previously or because other heart operations were planned They had all taken anticoagulants since the operation

Antithrombotic study The patients received either one gm of microencapsulated ASA (Colfarit Bayer AG Wupperthal West Germany) daily or placebo according to randomization the study being double blind The patients were strictly informed not to take any other preparations containing ASA a list with all forbidden preparations being given to them All patients received anticoagulant therapy, the intensity of which was controlled by Thrombotest (TT)[11] aiming at levels of 10% of normal activity

We had decided that ASA or placebo should be discontinued after all acute complications except those related to thromboembolism or cardiocirculatory performance This was done in order to avoid possible undesired effects of the combined therapy

The patients were examined after one and finally after two years A clinical examination was done x ray of the heart and lungs was performed and an ECG and several routine blood tests were taken Three stool specimens from each patient were examined for occult blood by the benzidine method and plasma salicylate levels were determined The few patients that were unable to meet were controlled by local physicians or hospitals and questionnaires were sent to the doctors of all patients in order to obtain complete information

The diagnostic criteria used for thromboembolic complications and a more detailed description of the management of the study have been published earlier[9]

Table I Bleeding complications in patients receiving ASA and anticoagulants and in patients on anticoagulants alone

	Patients treated with			
	ASA and anticoagulants		*Placebo and anticoagulants*	
Type of bleeding	*Episodes*	*Deaths*	*Episodes*	*Deaths*
Intracranial	2	1	3	2
Gastrointestinal	11		2	
Other	2		1	
Total	15	1	6	2

Platelet functions Platelet counts platelet retention in glass bead columns and bleeding time were determined in 16 patients with bleeding complications either before the study started or after discontinuation of ASA or placebo when the patients had recovered completely from the effects of blood loss The results were compared with those from unselected patients without bleeding complications All patients received anticoagulants when tested

Platelets were counted in a hemocytometer using a modification of Nygaard s method[4] Platelet adhesiveness was estimated from retention in glass bead columns according to the modified method of Hellem[5] The bleeding time was measured from two incisions by a modification of Ivy s method[2] The length of the cuts was approximately one cm and the depth adjusted so that a drop of a matchhead s size emerged in 30 seconds

Results

The combined therapy was given to 75 patients while 73 received placebo and anticoagulants

Bleeding complications were more frequent in patients on ASA and anticoagulants than in those on anticoagulants alone (Table I) the incidence being 13 9 and 4 7 episodes per 100 patients per year respectively The difference is statistically significant ($p < 0 02$) The difference is entirely due to the significantly higher incidence of gastrointestinal hemorrhage ($p = 0 01$) in the former group of patients Intracranial bleeding which was the most serious complication was not more frequent in patients who received ASA in addition to anticoagulants It

Table II Bleeding complications classified according to the effect on whole blood hemoglobin (hb) concentration (intracranial hemorrhage is not included)

Lowest hb concentration	*Patients treated with*	
	ASA and anticoagulants	*Placebo and anticoagulants*
Lower than 8 g/dl	5	2
8 to 11 g/dl	6	
Higher than 11 g/dl	2	1

Table III TT values before bleeding episodes in the two groups of patients with aortic ball valve prostheses

TT % of normal	*Patients treated with*	
	ASA and anticoagulants	*Placebo and anticoagulants*
Lower than 5	4	2
6 to 10	9	4
11 to 15	1	
16 to 20	1	

Table IV Relation between the intensity of anticoagulant therapy and the severity of bleeding (intracranial hemorrhage is not included)

TT before bleeding	*No of patients with hb concentration*		
	>11 g/dl	*8 11 g/dl*	*<8 g/dl*
Lower than 5%			4
6% to 10%	2	5	3
11% to 15%		1	
16% to 20%	1		

caused one death in patients on combined therapy and two in the placebo group

The patient taking ASA had for some weeks clinical signs of sepsis before she died from intracranial hemorrhage and autopsy revealed that the bleeding had occurred in a septic locus In a second patient on combined therapy and subdural hematoma developed less than one week after the start of the study but this 56 year old woman recovered completely after operation

In the placebo group a 53 year old man died after two days in deep coma At autopsy a subdural hematoma as well as an embolus in the middle cerebral artery was found There was

Table V Time relationship between the start of the study and the onset of bleeding

Time from start of therapy until bleeding	*Patients treated with*	
	ASA and anticoagulants	*Placebo and anticoagulants*
Less than 1 week	3	
1 week to 1 month	4	
2 to 6 months	2	2
7 to 12 months	4	2
13 to 18 months		1
19 to 24 months	2	1

however no connection between bleeding and embolus and no history of trauma could be revealed It was regarded most likely that the bleeding had occurred first and was of the greatest significance Two other men on anticoagulants alone suffered from intracranial hemorrhage, one died the other survived after surgical evacuation but with considerable functional disturbances The blood pressure was normal in all patients with intracranial bleeding

The severity of the other types of bleeding episodes was estimated from the lowest hemoglobin concentration after the hemorrhage (Table II) In five patients on combined therapy and two on anticoagulants alone Hb fell below 8 g/dl and blood transfusions were required The blood loss was gastrointestinal in these seven patients and all of them recovered completely

Only two of the bleeding episodes in the group receiving combined therapy occurred after TT values higher than 10% (Table III) The TT values of all patients throughout the observation period were reflected by those found at the annual controls In comparison only 33% of all values in patients on combined therapy and 28% in those on anticoagulants alone were 10% or lower The differences between the proportions of low TT values before bleeding and at annual controls were highly significant in both groups of patients ($p < 0.01$) The episodes of intracranial bleeding all occurred at TT values of 9% or lower Thus intense anticoagulant therapy was associated with an increased risk of bleeding particularly when ASA was given

The severity of the bleeding episodes was related to the intensity of the anticoagulant therapy before hemorrhage (Table IV) The results indicate that the blood loss at low TT

Table VI Comparison of platelet functions in patients with and without bleeding episodes with level of significance

	Patients with bleeding			*Patients without bleeding*			
	No	*Mean*	*S.E.M*	*No*	*Mean*	*S.E.M*	*p*
Platelet per μl	19	176 400	13 900	133	191 300	5 000	N.S
Adhesiveness, %	16	24.3	2.3	67	35.4	2.5	$p < 0.05$
Bleeding time min	16	6.9	0.5	24	6.7	0.4	N.S

values regardless of ASA ingestion tended to be particularly abundant. Thus Hb fell below 8 g/dl during all episodes in patients with TT at 5% or lower and two of the five episodes of intracranial bleeding occurred at such low TT values.

The time from the start of the study until the onset of bleeding was recorded (Table V). Nearly half of the episodes developed during the first month of ASA ingestion and only two patients on combined therapy bled during the second year of the study. In the placebo group, however, the six episodes were scattered throughout the observation period as could be expected since the patients had received anticoagulants constantly since the operation.

Platelet counts were moderately but insignificantly lower in the patients who developed bleeding episodes than in the others and the bleeding time did not differ significantly between the groups (Table VI). Platelet retention in glass bead columns, which is considerably reduced in patients with prosthetic ball valves, was significantly lower ($p < 0.05$) in patients with bleeding episodes than in those without.

Occult blood loss was detected in 12 of the 47 patients who remained on combined therapy until the end of the study, and in three of the 53 patients of the placebo group.

Discussion

The study revealed a higher incidence of bleeding episodes in the ball valve patients who received ASA in addition to anticoagulants than in those given equally intensive anticoagulant therapy alone. The rate of complications was, however, acceptable in view of the effective protection achieved against arterial thromboembolism with the combined treatment.[8] Moreover, the higher incidence was entirely attributable to gastrointestinal bleeding from which all recovered.

Bleeding complications are not rare in patients who receive anticoagulants after valve replacement and intracranial hemorrhage, which is particularly serious, did not occur more frequently in our study than in others.[2, 33] A comparable antithrombotic effect was demonstrated in a simultaneously performed study on valve patients as in our trial,[10] while the incidence of bleeding was similar in these two groups and slightly lower than in our patients given combined therapy. The daily dose of ASA was 0.5 gm and the anticoagulation aimed at TT values of 8 to 15%, but the intensity was not further documented. The combination of dipyridamole and anticoagulants offered a good antithrombotic effect in a previous trial in ball valve patients, but lethal intracranial bleeding occurred in two of 79 patients in one year while gastrointestinal hemorrhage did not occur.[3]

The thrombotic and hemostatic mechanism and the interactions between platelets and anticoagulation are complex.[1] Thus platelet phospholipoproteins exposed by the platelet release reaction accelerate the intrinsic coagulation system with the formation of thrombin, which is a potent inducer of just the platelet release reaction. ASA and anticoagulants affect thrombosis and thereby hemostasis on different levels. ASA inhibits irreversible platelet aggregation by inhibiting the enzyme cyclo-oxygenase, preventing the production of labile endoperoxides which are strong inducers of the release reaction.[34] Anticoagulants lead to a diminished production of some coagulation factors and thereby to reduced thrombin formation after activation of coagulation. One could therefore expect an additive or even synergistic effect on arterial thrombosis and hemostasis by these drugs. The reduced adhesiveness of the platelets, a reactivity involved in primary hemostasis, might further potentiate the inhibitory effect on thrombosis and hemostasis.

Consequently a particularly high incidence of bleeding complications could be feared in patients given combined therapy since hemostasis would be affected in three different ways.

The prevention of arterial thromboembolism must be weighed against the increased risk of bleeding and our study represents a step in the search for a therapy that may offer a satisfactory protection against arterial thrombosis at an acceptable risk of bleeding. Whether this can be achieved by intensive anticoagulant therapy or by large doses of ASA or by a combination of the two in more conventional doses, can only be determined in clinical trials.

The influence of each of the two drugs of the reduced platelet reactivity may to some extent be analyzed from our results. Thus the dose of ASA [illegible] undoubtedly increased the bleeding tendency but apparently only from the gastrointestinal tract. Such bleeding is also well known to occur after ASA ingestion even in patients without anticoagulants and with a presumably normal platelet function. [illegible] This indicates that local irritation of the mucosa either from the normal gastric content [illegible] from ASA liberated in spite of the microencapsulation is important in addition to the general [illegible] on hemostasis. Bleeding may be more easily precipitated in some patients than in others because their platelets might be particularly sensitive to the effects of ASA.[illegible]

The role of anticoagulants for the occurrence of bleeding complications also seems obvious. Thus, bleeding correlated with the intensity of the therapy as judged from the TT levels before the episodes. And equally important the severity of bleeding was related to the intensity of the treatment. Intensive anticoagulation was therefore without doubt responsible for several serious bleeding episodes. In a study on the effects of intensive anticoagulant therapy in coronary heart disease a condition with near normal platelet function bleeding episodes occurred almost as frequently as in our patients using combined therapy. The majority of TT values were below 10% with a mean of 8% as compared to 11% in our trial. In studies with less intensive anticoagulation bleeding is less frequent. Standardization of reagents for control of anticoagulant therapy is difficult, and different thromboplastins give different results. The coagulation activity in percent of normal as measured with Thrombotest and Simplastin A roughly parallel each other while most other methods give considerably higher values.[illegible] Our results demonstrate the intensity of anticoagulant therapy is also important for the bleeding tendency when given in combination with ASA.

The role of the reduced platelet function is more difficult to evaluate. However the correlation between the number of adhesive platelets and the bleeding time[illegible] as well as the particularly marked prolongation when ASA is given to patients with a low platelet adhesiveness, suggest that the reduced platelet reactivity was of importance. The low number of adhesive platelets in patients who developed bleeding as compared to the others indicate that reduced platelet adhesiveness predisposed to hemorrhage. The considerably reduced platelet adhesiveness is not further diminished by ASA ingestion which demonstrates that the trauma by the valve and ASA influence different platelet functions.

Bleeding tended to occur shortly after the start of ASA administration which may have two possible explanations: the bleeding may be initiated as soon as the TT level drops according to unavoidable physiological variations, or some patients may be particularly susceptible to the effect of ASA. A combination of the two mechanisms is probably the most likely cause of early gastrointestinal bleeding at low TT values. The results indicate that the combined therapy can be continued more safely if it is tolerated for the first two months.

In conclusion the greater tendency towards gastrointestinal bleeding was acceptable in relation to the antithrombotic effect achieved with the combined therapy. The correlation between the intensity of anticoagulation and the incidence of bleeding raises a question which is the issue of a present investigation. Will a slightly less intensive anticoagulant therapy in combination with ASA offer an equally effective protection against arterial thromboembolism and will the bleeding tendency thereby be reduced?

Summary

Bleeding complications were evaluated in 14[illegible] patients with single Starr Edwards aortic ball valve prostheses in a study designed to prevent arterial thromboembolism. They received either one gm of ASA daily or placebo in combination with anticoagulants and were observed for two years. Only two embolic episodes occurred in

patients on combined therapy as compared to 12 episodes in the placebo group

Fifteen bleeding complications developed in patients receiving ASA seven during the first month Two patients suffered intracranial hemorrhage and one died the others recovered completely Six episodes occurred in patients on anticoagulants alone three intracranial complications caused two deaths The higher incidence of bleeding induced by the combined therapy was entirely due to gastrointestinal hemorrhage indicating that irritation of mucosa was important in addition to the ASA induced inhibition of hemostasis

The intensity of anticoagulation correlated significantly with the occurrence of bleeding and severe blood loss developed only after intensive therapy This raises the question whether a slightly less intensive anticoagulation in combination with ASA will maintain a satisfactory antithrombotic effect at a lowered risk of bleeding

Platelet adhesiveness which is partly responsible for primary hemostasis was reduced in the ball valve patients and more in those who bled than in the others

It is concluded that the higher incidence of gastrointestinal bleeding in patients who received ASA and anticoagulants than in those on anticoagulants alone was acceptable when compared to the antithrombotic effect achieved with the combined treatment

REFERENCES

1. Boston Collaborative Drug Surveillance Group Regular aspirin intake and acute myocardial infarction Br Med J 1 440 1974
2. Elwood, P C Cochrane A L Burr M L Sweetnam P M Williams G Welsby E Hughes S J and Renton R A randomized controlled trial of acetyl salicylic acid in the secondary prevention of mortality from myocardial infarction Br Med J 1 436 1974
3. Sullivan J M Harker D E and Gorlin R Pharmacologic control of thromboembolic complications of cardiac valve replacement N Engl J Med 284 1391 1971
4. Breddin K Uberla K and Walter F German Austrian multicenter two years prospective study on the prevention of secondary myocardial infarction by ASA in comparison to phenprocoumon and placebo Thromb Haemost. 38 168 1977
5. Harrison, M J G Marshall J Meadows J C and Ross Russel, R W Effect of aspirin in amaurosis fugax Lancet 2 743 1971
6. Loew D Wellmer H K Baer U Merguet H Rumpf P Petersen H Bromig G Persch W F Marx F J and von Bary S M Postoperative thromboembolie prophylace mit acetylsalicylsaure Dtsch. Med Wochenschr 12 565 1974
7. Salzman E W Harris W H and DeSanctis R W Reduction in venous thromboembolism by agents affecting platelet function N Engl J Med 284 1287 1971
8. Kincaid-Smith P Modification of the vascular lesions of rejection in cadaveric renal allografts by dipyridamole and anticoagulants Lancet 1 920 1969
9. Dale J Myhre E Storstein O Stormorken H., and Efskind, L. Prevention of arterial thromboembolism with acetylsalicylic acid A controlled clinical study in patients with aortic ball valves AM HEART J 94 101 1977
10. Altman R Boullon F Rouvier J Raca R de la Fuente L. and Falvaro R Aspirin and prophylaxis of thromboembolic complications in patients with substitute heart valves J Thorac Cardiovasc Surg 72 127 19 6
11. Mustard J F Kinlough Rathbone R L., and Packham M A Recent status of research in the pathogenesis of thrombosis Thromb Diath Haemorrh. Suppl 59 1 57 1974
12. Zucker M B and Peterson J Effect of acetylsalicylic acid other nonsteroidal anti inflammatory agents and dipyridamole on human blood platelets J Lab Clin Med 76 66 19 0
13. Berger S Salzman E W Merrill E W and Wong P S L. The reaction of platelets with prosthetic surfaces in Platelets Production function transfusion and storage Baldini M G and Ebbe S eds New York, 1975 Grune & Stratton Inc p 299
14. Kakkar V V Low-dose heparin in the prevention of venous thromboembolism—rationale and results in Moderne Thrombose prophylaxe Breddin K and Gross D eds Stuttgart—New York 1974 F K Schattauer Verlag p 71
15. Dale J Arterial thromboembolic complications in patients with Bjork Shiley and Lillehei Kaster aortic disc valves, AM HEART J 94 562 1977
16. Dale J Arterial thromboembolic complications in patients with Starr Edwards aortic ball valve prostheses AM HEART J 91 653 1976
17. Silvergleid A J Bernstein R Burton D S Tanner J B Silverman J F and Schrier S L Aspirin Persantin prophylaxis in elective total hip replacement Thromb Haemost 38 166 1977
18. Dale J and Myhre E Platelet functions in patients with aortic ball valves AM HEART J 94 359 1977
19. Steele P Weily H Davies H Pappas G., and Genton G Platelet survival time following aortic valve replacement Circulation 51 358 1975
20. Stuart R K McDonald J W Ahuja S P and Coles J C Platelet survival in patients with prosthetic heart valves Am J Cardiol 33 840 1974
21. Harker L A and Slichter S J Studies on platelet and fibrinogen kinetics in patients with prosthetic heart valves, N Engl J Med 283 1307 1970
22. Dale J Reduced platelet adhesiveness in patients with prosthetic ball valves Relation to adenosine diphosphate and mechanical trauma AM HEART J 94 562 1977
23. Owren P A Thrombotest A new method for controlling anticoagulant therapy Lancet 2 754 1959
24. Hellem A J The adhesiveness of human blood platelets in vitro Scand. J Clin Lab Invest 12(Suppl 51) 20 1960
25. Hellem A J Platelet adhesiveness in von Willebrand s disease—A study with a new modification of the glass bead filter method Scand J Haematol 7 374 1970
26. Borchgrevink C F., and Waaler B The secondary

bleeding time A new method for the differentiation of hemorrhagic diseases Acta Med Scand 162 361 1958

27 Cleland J and Molloy P J Thrombo embolic complications of the cloth covered Starr Edward prostheses no 2300 aortic and 6300 mitral Thorax 28 41 1973

28 Friedli B Aerichide N Grondin P and Campeau L Thromboembolic complications of heart valve prostheses Am Heart J 81 702 1971

29 Akbarian M Austen W G Yurchak, P M and Scanell J G Thromboembolic complications of prosthetic cardiac valves Circulation 37 862 1968

30 Reed G E Clauss R H Tice D A and Acinapura A J Five year experience with Magovern aortic prostheses Circulation 43 and 44(Suppl I) 73 1971

31 Gadboys H L Litwak R S., Niemetz J and Wisch N Role of anticoagulants in preventing embolization from prosthetic heart valves J A M A 202 282 1967

32 Beall A C., Bloodwell R D Bricker D L Okies J E Cooley D A and DeBakey M E Prosthetic replacement of cardiac valves Am J Cardiol 23 250 1969

33 Bryant L R., Trinkle J K., Spencer F C Danielson G K Shabetai, R and Reeves J T Cardiac valve replacement Results in patients with advanced disability J A M A 216 996 1971

34 Weiss H J Willis A L Kuhn D., and Brand H Prostaglandin E potentiation of platelet aggregation induced by LASS endoperoxide Absent in storage pool disease normal after aspirin ingestion Br J Haematol 32 257 1976

35 Soloway H B Drug induced bleeding Am J Clin Pathol 61 622 1974

36 Levy M Aspirin use in patients with major upper gastrointestinal bleeding and peptic ulcer disease N Engl J Med 290 1158 1974

37 Mills D G Borda I T Philp R B and Eldridge C Effects of in vitro aspirin on blood platelets of gastrointestinal bleeders Clin Pharmacol Ther 15 187 1974

38 Loeliger E A Hensen A Kross F van Dijk, L M Fekkes N de Jonge H and Hemker H C A double blind trial of long term anticoagulant treatment after myocardial infarction Acta Med Scand 182 549 1967

39 Owren P A The history of Thrombotest in Human Blood Coagulation Hemker H C Loeliger E. A., and Veltkamp J J eds Leyden 1969 Leyden University Press p 306

40 Owren P A Standardization of thromboplastin reagents and control plasmas, Haematologia 8 441 1974

41 Dale J Myhre E and Rootwelt K Effects of dipyridamole and acetylsalicylic acid on platelet functions in patients with aortic ball valve prostheses Am Heart J 89 613 1975

Excitation of ischemic myocardium altered properties of conduction refractoriness and excitability

Ronald R. Hope M B F R.A C P
Benjamin J Scherlag Ph D
Ralph Lazzara M D
Oklahoma City Okla

Conduction delays within the ischemic subepicardium have repeatedly been implicated in the genesis of ventricular arrhythmias in acute [1-6] subacute and chronic[7] myocardial infarction In the first few minutes after coronary artery ligation the heterogenous nature of the electrophysiological properties of the ischemic zone have been noted and closely correlated with the onset of ventricular arrhythmias.[5, 6] However because conduction and refractoriness change rapidly during this phase and because of the frequent interposition of lethal ventricular arrhythmias the ability to study the electrophysiology of acutely ischemic myocardium is limited A recent study by Elharrar and associates involved ventricular pacing in acute myocardial ischemia utilizing a pacemaker which determined diastolic threshold every 45 seconds These workers measured a gradient of excitability threshold between normal and ischemic myocardium within the first minutes of ischemia

We have previously reported that dogs with subacute myocardial infarction provide a more stable model for analysis of the association between epicardial conduction disturbances and ventricular arrhythmias[7-11] Employing this model we detected altered properties of conduction refractoriness and excitability of ventricular epicardium overlying the infarct zone in the period 3 to 10 days after myocardial infarction The relationship between these altered electrophysiological properties and induced rate-dependent myocardial arrhythmias was examined in the intact animal as well as at a cellular level This study set out to examine the mechanisms whereby such arrhythmias traverse the abnormal epicardium overlying the infarction zone and eventually reenter the normal myocardium

Materials and methods

Experiments were performed on 18 adult mongrel dogs weighing 10 to 30 kg and anesthetized with intravenous sodium pentobarbital (30 mg / kg) A Harvard respirator provided mechanical ventilation of the lungs with room air through a cuffed endotracheal tube A left thoracotomy in the fourth intercostal space was performed The pericardium was incised and the anterior descending cononay artery was exposed immediately below the origin of the anterior septal branch. A silk ligature was placed around the artery and the vessel was occluded In all 18 dogs including three sham operated dogs (not subjected to coronary artery ligation) the epicardium was repaired and the thoracotomy was closed Three to nine days later each animal underwent repeat thoracotomy using the same anesthetic and ventilatory procedures described above The pericardium was reopened The area of myocardial infarction was visually identified Three to five pairs of fine

From the Section of Cardiology Oklahoma University Health Science Center and Veterans Administration Hospital, Oklahoma City Okla.

Supported in part by National Institutes of Health Grant No HL-18130

Received for publication March 1., 1979

Accepted for publication May 11 1979

Reprint requests D Ronald R. Hope Director Coronary Care Unit and Heart Station, The University of Oklahoma Health Sciences Center Medicine/Cardiology Section, P O Box 26901 Oklahoma City Okla. 73190

bleeding time. A new method for the differentiation of hemorrhagic diseases Acta Med Scand 162 361 19[illegible]

27 Cleland J and Molloy P J Thrombo-embolic complications of the cloth-covered Starr Edward prostheses no 2300 aortic and 6300 mitral, Thorax 28 41 1973

28 Friedli, B., Acrichide N., Grondin P., and Campeau L. Thromboembolic complications of heart valve prostheses AM HEART J 81 702 1971

29 Akbarian M Austen W G Yurchak, P M., and Scanell J G Thromboembolic complications of prosthetic cardiac valves Circulation 37 862 1968

30 Reed G E., Clauss R H., Tice D A., and Acinapura A J Five year experience with Magovern aortic prostheses Circulation 43 and 44(Suppl I) 73 1971

31 Gadboys, H L., Litwak R S Niemetz J and Wisch N Role of anticoagulants in preventing embolization from prosthetic heart valves, J.A.M.A 202 282 1967

32 Beall A C., Bloodwell R D Bricker D L. Okies J E Cooley D A and DeBakey M E Prosthetic replacement of cardiac valves Am. J Cardiol. 23 250 1969

33 Bryant L. R., Trinkle J K., Spencer F C., Danielson, G K. Shabetai, R., and Reeves J T Cardiac valve replacement Results in patients with advanced disability J A M A 216 996 1971

34 Weiss H J Willis A L. Kuhn D., and Brand H Prostaglandin E potentiation of platelet aggregation induced by LASS endoperoxide Absent in storage pool disease, normal after aspirin ingestion Br J Haematol 32 257 1976

35 Solowav H B Drug induced bleeding Am. J Clin Pathol. 61 622, 1974

36 Levy M Aspirin use in patients with major upper gastrointestinal bleeding and peptic ulcer disease N Engl. J Med 290 1158 1974

37 Mills D G., Borda I T., Philp R B and Eldridge C. Effects of in vitro aspirin on blood platelets of gastrointestinal bleeders, Clin Pharmacol Ther 15 [illegible]

38 Loeliger E A Hensen A., Kroes, F van Dijk, L M Fekkes N de Jonge H and Hemker H C. A double blind trial of long term anticoagulant treatment after myocardial infarction Acta Med Scand. 182 549 19[illegible]

39 Owren P A The history of Thrombotest in Human Blood Coagulation Hemker H C Loeliger E. A., and Veltkamp J J eds. Leyden 1969 Leyden University Press p 306

40 Owren P A Standardization of thromboplastin reagents and control plasmas, Haematologia 8 441 19[illegible]

41 Dale J Myhre E and Rootwelt K. Effects of dipyridamole and acetylsalicylic acid on platelet functions in patients with aortic ball valve prostheses AM HEART J 89 613 1975

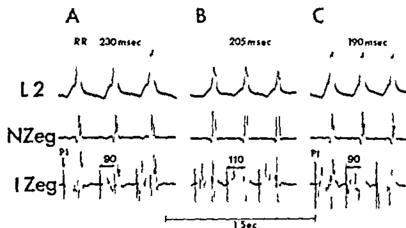


Fig 2 The effect of increasing heart rate and stimulus strength on epicardial conduction and QRS morphology in the infarcted dog heart Abbreviations are the same as in *Fig 1* Pacing is from the IZ at an RR cycle length of 230 msec. Note the fractionated activity preceding the QRS and coincident with the direction of the delta wave in the ECG The interval from the onset of the PI to the major deflection of the IZeg is 90 msec In *panel B* at a faster rate (RR of 205 msec) the PI to IZeg increases to 110 msec Concurrently the QRS morphology is altered In *panel C* by increasing the stimulus strength of the pacer from 8 to 9 volts the conduction time from the PI to the IZeg is reduced to 90 msec. and the QRS reverts to the morphology seen at the slower rate although the heart rate has actually been increased (RR = 190 msec)

During the procedure areas of maximum activation delay were sought within the subepicardium overlying the infarcted area This was achieved by varying the position of the bipolar wire electrodes within the subepicardium of the infarct zone In all experiments ventricular pacing from the superficial subepicardium was carried out from at least three (and as many as five) areas overlying the infarct zone The pacing techniques employed were the same as those used to pace from the normal myocardium Attempts at pacing from within the myocardium or deep subepicardium of the infarcted zones were invariably unsuccessful with plunge wire electrodes even at stimulus intensity as high as 150 volts and 10 to 20 msec duration Care had to be taken to place the plunge wire electrodes in the most superficial subepicardium in order to achieve ventricular pacing If during the various pacing procedures ventricular fibrillation occurred no attempt at resuscitation was made

Results

In dogs with subacute myocardial infarction ventricular pacing from normal myocardium was associated with regular capture and constant QRS morphology at rates as fast as 360 beats/minute Moreover the stimulus to QRS interval 15 to 20 msec was constant at all heart rates up to 360/minute In this report we directed our attention to the electrophysiological abnormalities in response to pacing stimuli delivered to the subepicardium overlying the infarction

When pacing the ventricle from the epicardium basic differences in activation were noted according to the site of stimulation in relation to normal or infarcted myocardium Fig 1 *panel A* illustrates electrograms *(eg)* from the normal zone *(NZ)* and from subepicardium overlying the infarct zone *(IZ)* together with electrocardiogram Lead 2 *(L2)* There is delay of conduction within the subepicardium overlying the IZ which manifests as fractionated and prolonged activation recorded by the IZeg Ventricular pacing from a site in the NZ *(panel B)* at the same rate (RR = 215 msec) is associated with little change in either NZeg or IZeg recordings Total activation time as measured from the IZeg is 125 msec In *panel C* pacing at the same rate from a subepicardial site close to the IZeg demonstrates early activation of the neighboring IZeg *(lower trace)* The QRS and NZeg are activated after a prolonged exit time from the IZ Total activation time is now 170 msec A "delta" wave appearance of the initial QRS upstroke is seen in the electrocardiogram The QRS was regularly deformed in this manner when pacing from the subepicardium overlying the infarction presumably due to delayed conduction with relatively slow spread of activation through this abnormal muscle When

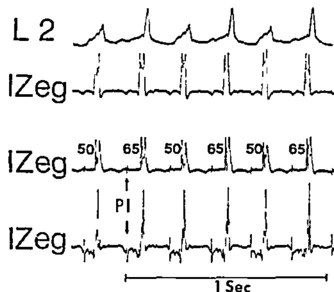


Fig 3 The effect of IZ pacing at a constant rate and stimulus strength on QRS morphology and IZ conduction Pacing from a particular site in the abnormal epicardium overlying the infarct in this experiment showed an alternating QRS morphology in the ECG coincident with an alternating conduction time from the pacer impulse *(PI)* to the various electrograms recorded in other portions of the abnormal epicardium *(three traces labeled IZeg)*

the impulse exits into the normal zone and conducts via normal pathways the remainder of the QRS is not inordinately delayed

For a given site of stimulation in the abnormal zone the time required for an impulse to exit from that abnormal zone and the pattern of ventricular activation depended on the rate and strength of stimulation In Fig 2 ventricular pacing (RR = 230 msec stimulus 8 volts) from the abnormal subepicardium is associated with prolonged conduction in this area The interval between stimulus and R wave (and normal zone activity) is approximately 90 msec Increasing the stimulus rate (RR = 205 msec) results in further conduction delay in the subepicardium overlying the infarction (110 msec) and an obvious change in QRS morphology Stimulus strength in panel C has been increased to 25 volts and the conduction time within the abnormal zone and QRS configuration have reverted to values shown in panel A This has occurred in spite of a further increase in pacing rate (RR = 190 msec) In all animals studied ventricular pacing from one or more abnormal zone sites resulted in changes of QRS morphology dependent upon rate and strength of stimulation

Fig 3 illustrates alternation of exit pathways in the subepicardium overlying the infarction Stimulation strength (8 volts) and rate are constant This pacing rate (RR = 210 msec) is associated with alternation of QRS patterns and of conduction time from stimulus to all ventricular electrograms but the measured values (msec) are shown for the lower IZeg only This phenomenon of alternation of QRS morphology and/or infarct zone conduction time was seen in 24% of our experiments over a narrow range of pacing rates These rates varied from one animal to another and also depended upon the strength of the stimulus

When pacing from the normal ventricular subepicardium conduction delay within the abnormal zone was observed but complete entrance block to any particular IZ site was never seen In contrast pacing from the subepicardium of the infarct zone resulted in block to the normal zone and failure to capture the ventricle Fig 4 is from the same experiment as is illustrated in Fig 3 However the pacing stimulus strength is reduced (6 volts) and the rate is faster (RR = 195 msec) Conduction time from the stimulus to the IZ electrogram has increased to 75 msec At the same pacing rate but with stimulus strength reduced to 4 5 volts *panel B* demonstrates failure to achieve capture with alternate stimuli In this instance as in others it was not possible to determine if these observations were due to failure of excitation by alternate stimuli or to exit block from the subepicardium over the infarct zone surrounding the pacing bipole It may also be noted that when ventricular capture occurs there is a change in QRS configuration and improvement in abnormal zone conduction (55 msec) presumably due to the relative slowing of the heart rate

Figs 5 and 6 indicate some of the varied ways in which during ventricular pacing from the subepicardium overlying the infarction (with constant stimulus strength and rate) spontaneous failure of pacing was observed In Fig 5 in *panel A* electrocardiogram Lead 2 *(L2)* and one infarct zone electrogram *(IZeg)* are shown The panel illustrates a sequence of Wenckebach conduction delay from the stimulus to the electrogram in the abnormal subepicardium and ultimate failure of capture by the pacing stimulus Prolongation of conduction time between stimulus and onset of abnormal zone activation (in this particular site) gradually increases from 10 to 32 msec before block occurs In *panel B* at a relatively slow

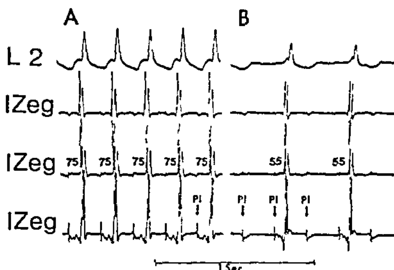


Fig 4 The effect of pacing from the abnormal epicardium at rapid heart rates on QRS morphology and conduction in the IZ. This figure is a continuation of the traces shown in *Fig 3*. In *panel A* the stimulus strength has been reduced to 6 volts and the heart rate increased to a cycle length of 195 msec. Note that the conduction from the pacer impulse *(PI)* to the onset of the middle electrogram remains constant at 75 msec. In *panel B* the stimulus strength was further reduced to 4.5 volts resulting in a 2:1 relationship between pacer impulses and ventricular activation. In every alternate beat the conduction time from the pacer impulse to the IZeg is 55 msec and the QRS morphology is different from that seen in panel A. See text for further discussion.

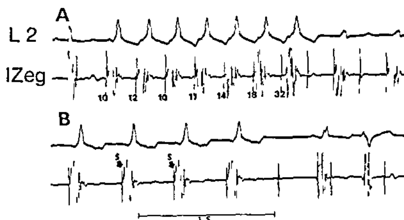


Fig 5 Two forms of activation failure seen during pacing from the abnormal epicardium in the infarcted dog heart. In those panels ECG *(L2)* and an electrogram from the abnormal epicardium *(IZeg)* are shown. In *panel A* ventricular pacing initiated at a constant rate after the first sinus beat shows progressive increase in the conduction time from the pacer impulse to the onset of the QRS complex as well as a similar delay in the interval between the pacer impulse and the onset of the IZeg. When the delay reaches a maximum of 32 msec block is seen in the next beat with subsequent occurrence of 2:1 ventricular activation. Note the change in QRS morphology between the 1:1 and 2:1 sequences. In *panel B* at a constant pacing rate (RR = 390 msec) there is a sudden loss of excitation after the fifth paced impulse. However this is not preceded by any measurable change in the interval between the pacer impulse and onset of the QRS or the IZeg. See text for details.

heart rate (RR = 390 msec) the fifth and subsequent stimuli *(S)* abruptly fail to achieve ventricular capture. Preceding infarct zone electrograms are stable. The initial stimulus which fails to capture is well beyond the T wave of the previous beat. This example of apparent sudden excitation failure may also be a result of prolonged (post repolarization) refractoriness (also see Fig 7).

In Fig 6 *panel A* at a constant pacing rate the pacing impulse *(PI)* abruptly fails to capture the

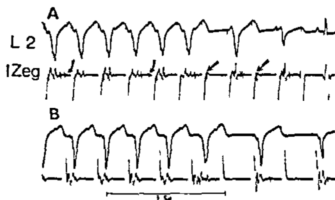


Fig 6 Presumptive evidence for conduction versus excitation failure during pacing from the abnormal epicardium of the infarcted dog heart Labels are the same as in *Fig 5* In *panel A* pacing from a site in the abnormal epicardium at an RR interval of 220 msec does not result in any marked alteration in the QRS complex however the electrogram recorded from a given site in the abnormal epicardium shows marked fractionation of local activation from beat to beat Note *curved arrows* The sudden failure of ventricular activation is characterized by a pacer impulse followed by local activation of the IZeg *(straight arrow)* suggesting conduction block even though the pacer impulse falls during the refractory period of the ventricles In *panel B* from another experiment during ventricular pacing from the abnormal epicardium and an RR interval of 270 msec the IZeg shows relatively constant activation until the beat prior to the block which shows marked prolongation and fractionation of the local ventricular activation This was followed by a pacer impulse and no recordable activation Coincidentally no ventricular activation was seen even during the subsequent 2 1 sequence

ventricle after the sixth beat in the panel despite excitation of the abnormal zone A complex pattern of delayed electrical activity is seen within the abnormal zone (RR = 220 msec) At times delayed electrical activity can be seen in late diastole *(curved arrows)* After the sixth beat abrupt loss of ventricular capture occurs with alternate stimuli On examination of the surface electrocardiogram *(L2)* it might be supposed that the stimulus occurring early during the T wave failed to excite the myocardium due to absolute ventricular refractoriness In this case however there is not a failure of excitation within the infarct zone because electrical activity is observed *(straight arrow)* following the stimulus artifact Thus there is direct evidence for concealed conduction in the subepicardium over the infarction and also for exit block of conduction in the abnormal zone *Panel B* shows another pattern of altered response to regular ventricular stimulation (RR = 270 msec) Infarct zone electrograms are relatively unchanged until abrupt lengthening of conduction time occurs in the sixth beat The interval between the pacing impulse and the QRS of beats one through five is 70 msec but abruptly lengthens to 120 msec in the sixth beat The next stimulus fails to capture

All dogs demonstrated abrupt failure of ventricular pacing in the manner shown in Figs 5 and 6 from at least one subepicardial site overlying the infarction Wenckebach conduction delay with resultant exit block and failure of pacing (Fig 5 *panel A*) was observed in 40% of the studies Sudden excitation failure with inability of the stimulus to achieve ventricular capture (Fig 5 *panel B*) occurred in 10% of the dogs Accurate quantitative assessment of less frequently observed phenomena (e g Fig 6 *panel B*) would however require pacing from multiple infarction zone areas at different rates and stimulus strengths

The complex and heterogeneous aspects of infarct zone refractoriness are illustrated in Fig 7 *Panels A* through *F* depict the response of the ventricle to a premature ventricular stimulus introduced into the subepicardium overlying the infarction during otherwise regular ventricular pacing (RR = 320 msec) from the same stimulation site The coupling interval of the premature stimulus is gradually shortened from 175 msec *(panel A)* to 145 msec *(panel F)* In *Panel A* the premature stimulus has resulted in ventricular capture However the configuration of the next beat in the series of regularly paced ventricular beats has altered (fourth beat in panel) In *panels B* and *C* the fourth beat becomes less distorted as the coupling interval of the preceding premature beat (third beat) is shortened This may be explained on the basis of a prolongation of refractoriness outlasting the T wave—i e postrepolarization refractoriness resulting from a preceding long short cycle sequence[17] In this instance the duration of the postrepolarization refractoriness must approximate the interval between beats three and four of *panel C* In *panel D* it can be appreciated that with further shortening of the premature stimulus coupling interval there is obvious prolongation and fractionation of activity recorded in the area of the electrogram (contrast the duration of the IZeg of the premature beat in panels A and D) Prolonged abnormal zone conduction results in a reentrant beat *(panel E)* with continuous activity recorded by the IZeg Note in panel E that abbreviated myocardial refractoriness exists as demonstrated by the inability of the stimulus to excite even when introduced

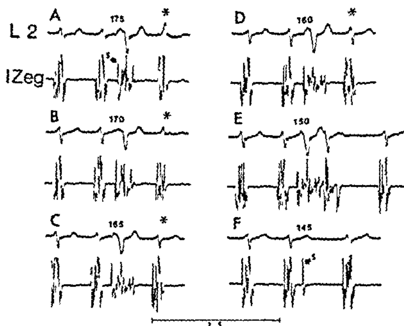


Fig 7 Coexistence of markedly shortened and markedly prolonged refractoriness in the abnormal epicardium of the infarcted dog heart. Two traces, ECG Lead II *(L2)* and an electrogram from the abnormal epicardium *(IZeg)* are shown in all panels *(A* to *F)* During ventricular pacing from a site within the abnormal epicardium at a cycle length of 370 msec premature ventricular stimuli *(S)* are introduced with increasing prematurity in each consecutive panel Note in *panel A* that a premature ventricular beat introduced at a coupling interval of 175 msec shows marked fractionation of the IZeg In addition the next driven beat *(asterisk)* shows a different morphology than the previous QRS at the basic driving cycle length This effect seen in *panels A* through *D* may indicate postrepolarization refractoriness in the abnormal epicardium In *panel E* excitation by a premature ventricular beat at a 150 msec coupling interval occurs even though the stimulus is delivered on the upstroke of the preceding T wave indicating markedly shortened refractorines. This very early excitation leads to marked fractionation of the IZeg and subsequent reentry beat *(panel E)* In *panel F* at a coupling interval of 145 msec a period of absolute refractoriness has been approached and no ventricular excitation occurs in response to the premature stimulus

prior to the onset of the T wave of the preceding beat Eventually *(panel F)* at a coupling interval of 145 msec absolute refractoriness of the abnormal subepicardial muscle is encountered and the stimulus is seen without consequent ventricular capture Thus the figure illustrates the simultaneous existence of both abbreviated absolute refractoriness of subepicardial muscle within the infarct zone as well as prolonged postrepolarization refractoriness induced by sudden alteration of regular rhythm [11]

Fig 8 shows in vitro observations which relate to some of the preceding in vivo findings A diagrammatic representation of the experiment is shown in the *upper left The stippled area* represents the infarct zone *(IZ)* to which pacing stimuli were applied Intracellular potentials and electrograms were recorded from the epicardium of normal and infarcted areas *(1* and *2* respectively) In *panel A* intracellular action potentials and electrograms from both infarct and normal zones are shown during epicardial pacing over the infarct zone at a cycle length of 800 msec Even at this cycle length the IZ intracellular potential shows decreased amplitude and duration in comparison to the IZ action potential In *panel B* the pacing cycle length was shortened to 600 msec The IZ intracellular potential is markedly deformed and conduction to the NZ is prolonged in comparison to panel A Note also in *panel B* in *the bottom tracing* that the electrogram recorded in the ischemic zone shows no activity apart from a stimulus artifact This occurs in spite of the close proximity of this electrogram to the microelectrode recording site within the infarct zone epicardium In *panel C* the driving cycle length was shortened further to 400 msec No activity is recorded in either normal or infarct zone electrograms and the cell in the normal zone remains quiescent The ischemic zone action potential diminishes in amplitude and duration to the brief response shown in panel C With further short

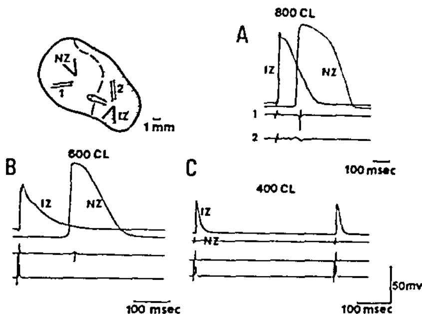


Fig 8 A comparison of the transmembrane action potential record in NZ and IZ from a portion of excised epicardium studied in vitro The diagram *at upper left* indicates the extracellular and intracellular recording sites in the NZ and IZ *(stippled area)* Stimulation was performed from the IZ 1 to 2 mm from the recording sites. In *panel A* action potentials and electrograms from the IZ and NZ at a cycle length of 800 msec are shown In *panels B* and C the pacing cycle length was decreased to 600 and 400 msec., respectively Note the increasing degree of delay and block between IZ and NZ, as well as the loss of amplitude and duration of the IZ action potential. See text for discussion.

ening of the cycle length the response diminished further gradually becoming indistinguishable from a stimulus artifact Further recordings from this experiment are shown in the next figure

In Fig 9 illustrations are taken from the same experiment as shown in Fig 8 Again in panels *A* to *C* pacing is from the abnormal epicardium overlying the infarct zone as shown in Fig 8 and the cycle length is progressively shortened from 320 msec *(panel A)* to 300 msec *(panel B)* to 285 msec *(panel C)* In *panel A* the four tracings depicted are from top to bottom infarct zone and normal zone intracellular action potentials and normal zone and infarct zone electrograms At this cycle length (320 msec) the infarct zone intracellular action potential is markedly abnormal and is seen to be abbreviated both in duration and amplitude when compared to the intracellular recording from the normal zone Furthermore a progressive decrease in amplitude and an increase in notching of the abnormal zone action potential is seen in the first fou beats of this panel followed b failure of excit tion by the fifth stimulus when only a stimulu artifact is apparent The sixth stimulus excite- and there appears to be some recovery of th a rormal zone cell In *panel B* the cycle length h s ' n short ened further to 300 msec and a 2 1 excitation pattern is seen in the behavior of the cell in this zone With further shortening of the cycle length to 285 msec in panel C there is higher degree excitation failure with abnormal zone pacing No extracellular activation is seen after delivery of the first two stimuli The third stimulus gives rise to a distorted low amplitude and abbreviated action potential within the abnormal zone Conduction to neighboring areas is noted *(lower electrogram)* and to the normal zone where healthy intracellular recording and normal electrogram response occurs In the case of the first and second stimuli in panel C it is uncertain whether or not the intracellular response recorded within the abnormal cell represents an aborted abnormal action potential (spike potential") or simply a stimulus artifact The fourth stimulus clearly gives rise only to a stimulus artifact a A may represent prolonged (postrepolarization) refractoriness following the abnormal action potential induced by the preceding stimulus.

Discussion

Reentry as a mechanism of cardiac arrhythmias has been invoked since the experiments of Mayer using the jellyfish umbrella ' as cited by

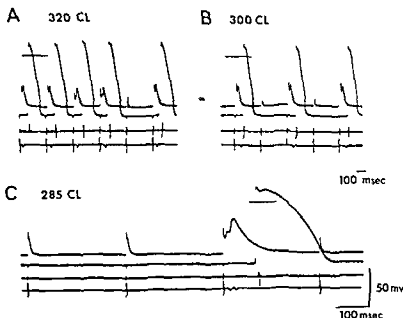


Fig 9 The effects of decreasing cycle length on delay and block between IZ and NZ In *panel A* and *B* at cycle lengths of 320 and 300 msec various degrees of block between IZ and NZ are characterized by diminution of action potential amplitude and duration In *panel C* the first two diminutive action potentials under the stimulation electrode do not produce local excitation Note the presence of IZ electrogram activation associated with a fractionated action potential following the third stimulus The fourth stimulus is followed by a passive membrane response See text for discussion

Cranefield (see Ref 29 chapter 5) The theoretic criteria for reentry namely slow conduction and unidirectional block were firmly established by the work of Schmitt and Erlanger [19] Experimentally the work of Moe and associates[20] laid the foundation for the clinical demonstration of reentry whereas the recent work of Wit and colleagues[2, 22] and Anderson and co workers [3] provided clear evidence for reentrant arrhythmias in the His Purkinje system These latter studies involved the use of normal tissues intoxicated by hyperkalemia and high doses of catecholamines

Only since 1969 has the evidence been gathered to establish reentry as a mechanism of arrhythmias in ventricular muscle undergoing acute myocardial ischemia [1, 7, 24] The transient nature of these arrhythmias[2, 5, 28] has not allowed detailed investigation of the alterations in electrophysiological properties responsible for reentry These reports have emphasized the difficulty in studying such transient phenomena Studies in our laboratories have described the existence of conduction defects in the epicardium of the infarcted dog heart three to 10 days after coronary artery ligation [7, 8] Directly associated with these conduction abnormalities is the spontaneous occurrence of reentrant ventricular arrhythmias which can be induced by various interventions [7, 8] This electrically stable state of myocardial abnormalities related to infarction permits the systematic study both in vivo and in vitro of the alterations in excitability conduction and refractoriness[16, 27] underlying reentry in tissue adjacent to areas of recent infarction It should be pointed out that these findings were determined in sick but viable subepicardium Recording and pacing from deeper layers indicated dead tissue—i e truly infarcted It would be difficult to call the subepicardium overlying the infarction ischemic since blood flow was not measured However in vitro the abnormal properties were unchanged even after prolonged periods of superfusion If superfusion during the microelectrode studies had provided insufficient flow for the abnormal areas these cells would have deteriorated as would those of the normal zone Neither showed significant deterioration over 3 to 4 hours of study If in vitro superfusion represented flow over and above perfusion in vivo the abnormal zone might have been expected to have shown steady improvement This did not

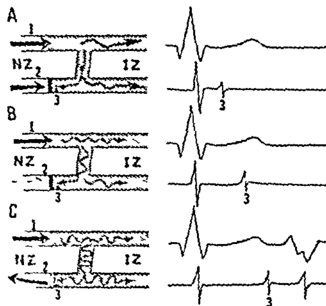


Fig C schematic representation of functional dissociation ... conduction and reentry in two pathways of ventricular muscle. The pathways are labeled *1* and *2* and the electrocardiogram and electrogram recorded at site 3 are shown on the right. The first impulse enters pathways 1 and 2 *(panel A)* and encounters slow conduction *(stippled area pathway 1)* and total block *(solid vertical bar pathway 2)*. In *panels B* and *C* the next two impulses entering at pathway 1 encounter progressively slower conduction (*note* increased tortuosity of path ... through stippled area). In *panel C* point 3 is activated ... enough to allow re-entry. See text for further discussion.

occur. It would appear then that the processes of ischemia and infarction induced, as a secondary effect, alterations of the electrical properties in those tissues surviving infarction.

Our previous reports utilizing recordings from the epicardium of the infarcted region have provided crucial direct evidence for reentry—i.e. continuous electrical activity bridging the interval between normal and ectopic beats. Also the effect of rate and rhythm to enhance or diminish such continuous activity has been demonstrated. In the present study pacing from the subepicardium of the infarcted area has allowed further characterization of the electrophysiology of the abnormal tissues. In contrast to pacing from normal myocardium, pacing from the abnormal subepicardium manifested unusual responses. At a constant stimulus strength pacing from the same site caused different QRS complexes as a function of pacing rate. Each form of QRS was associated with a different latency—i.e. the time from the stimulus to the onset of the QRS complex. Actually ... ng time interval was found to represent ... duction within the abnormal subepicardium. Evidence for this view was the increase in duration of the delta wave preceding each type of QRS complex as the heart rate increased (see Fig 2). Also recording near the stimulating electrode or between the stimulating electrode and the normal zone electrogram showed continuous electrical activity starting at the stimulus and extending up to the onset of the QRS complex (Fig 1). This fractionated activity was temporally consistent with the delta wave preceding the QRS complex. In vivo the areas of greatest delay, as the heart rate was increased, were within the abnormal epicardial muscle overlying the infarct zone.

Normal conduction in most areas of the ventricle is dependent on impulse transmission through both fast (His Purkinje system) and slow (ventricular muscle) pathways. Since previous work in the dog with transmural infarction has indicated *that muscle underlying the endocardium is inexcitable,*[16] and in our studies *the deeper subepicardial muscle was also inexcitable, it can be assumed that conduction must proceed only through the epicardium which overlies the infarcted muscle as a thin rim of abnormal but viable tissue. This would account for the slow transit time and the delta wave (Fig 1) preceding the onset of the major QRS deflection—the latter representing more rapid activation via His Purkinje and normal muscle tissue. Some other facets of altered conduction in this area were seen which relate to reentry. Functional dissociation of conducted impulses exiting from the abnormal zone was frequently noted in vivo, particularly in response to increasing heart rate. Interestingly in Fig 3 at a constant heart rate the conduction to each of the electrograms alternated. Such a finding indicates that at least two conduction pathways were involved between the abnormal and normal zones (possibly multiple pathways) at this rate and this could account for the different QRS complexes seen. Furthermore the dissociation of conduction into separate pathways, some of which showed intermittent block, clearly favors reentry. This view has been postulated by Ashman and Hull[?] for myocardial infarction and has been elaborated by Cranefield ... reentry can not occur within an infarct unless there is some partially isolated pathway in which conduction can occur in only one direction. If the island is invaded from all sides by excitatory impulses those impulses may travel very slowly within the infarct but they will eventually collide with each*

other and be extinguished without reentering the ventricle It is for that reason among others that the mere demonstration of delayed excitation within an infarct does not constitute satisfactory evidence that a premature impulse arising near the infarct is caused by reentry via a pathway through the infarct [7-9]

Although the evidence for unidirectional block between NZ and IZ was consistently observed the nature of the block was not easily discerned Observed frequently however was the occurrence of Wenckebach Mobitz II and paroxysmal (repetitive) forms of block from the IZ to the NZ particularly as a function of rate In previous reports the close relationship between delay of epicardial activation in a Wenckebach fashion and the occurrence of reentry beats has been documented [10, 11] Although Wenckebach periodicity can invariably be induced in the normal A V node during antegrade conduction [30] it is seldom associated with reentry If one combines Wenckebach periodicity repetitive block and functional dissociation manifest reentry now becomes easier to construct In Fig 10 a schematic representation of a simplified model of reentry is shown In three successive beats (*A* to *C*) at a critical heart rate conduction velocity progressively slows in pathway 1 (in the form of a Wenckebach cycle) during three beats (*A* to *C*) However at this rate pathway 2 exhibits repetitive antegrade block (as shown in Figs 8 and 9) of the impulse *(vertical bar)* This functional dissociation allows the point labelled *3* to be activated later in the Wenckebach cycle *(panel B)* When *area 3* is activated late enough that its appearence follows the T wave (after the area of repetitive block has repolarized) retrograde invasion of the NZ occurs resulting in a reentrant beat Under these circumstances of repetitive (unidirectional) block the concurrent Wenckebach period will culminate in a ventricular ectopic beat coupled to the sinus beat in a repeatable trigeminy [12] If on the other hand there is occasional conduction in pathway 2—i.e intermittent loss of repetitive block this intermittent conduction could interfere with the Wenckebach type pattern thus inhibiting manifest reentry and producing concealed reentry

Coexistence of various forms of block were matched by the *observation that very short and* very long refractoriness could co exist in abnormal tissues In Fig 7 late coupled ventricular premature contractions arising in the abnormal zone resulted in a change in the QRS configuration of the next driven beat even though the basic cycle length (330 msec) exceeded the QT interval by 140 msec This is an example of postrepolarization or markedly prolonged refractoriness noted previously in ischemic myocardium [17, 31] At shorter coupling intervals marked fractionation and delay were recorded in the IZ electrogram indicating slow conduction due to activation of some pathways during their relative refractory period The ischemic zone could be depolarized as early as the onset of the T wave and using stimuli less than two times the diastolic threshold which is earlier than can be achieved with stimulus intensities between 10 and 12 times threshold prior to the peak of the T wave in the normal heart [29] In vitro findings of abbreviated action potentials (Figs 8 and 9) provided one possible explanation for these unusually short refractory periods

What is the possible significance of this simultaneous but opposing change in refractoriness in the abnormal zone? Firstly activation during the relative refractory period occurring early or late in the cardiac cycle causes slow conduction (see above) which favors reentry Recent experimental work in our laboratory was documented the occurrence of reentry ventricular arrhythmias triggered by late coupled beats as well as by early coupled beats Clinical reports have now recognized the arrhythmogenic potential of early and late coupled premature ventricular contractions Secondly the occurrence of the V on V phenomenon[36] so commonly seen preceding ventricular fibrillation can be explained on the basis of the shortened refractoriness in some areas of the ischemic zone A recent clinical report[3] clearly documents the very early occurrence of premature ventricular beats even at the onset of the T wave The coexistence of long and short refractoriness (Fig 7) is another indication of the marked heterogeneity in the electrophysiological properties of ischemic tissue Han and Moe popularized the concept of dispersion of refractoriness as an important determinant of reentrant arrhythmias However in their studies as well as in more recent work by Levites and associates[2] the greatest dispersion of refractoriness measured only 40 msec In the present study dispersion of refractoriness *of at least 150 msec can be appreciated* in Fig 7

Many of the electrophysiological responses of myocardial cells have been extensively studied only in normal zones Some of these responses

may be modified in abnormal epicardium overlying infarcted zones. For example the action potentials of myocardial cells in these abnormal areas were often of bizarre configuration (Fig 8) These deformed and fractionated action potential responses have been reported previously [31] and in our experiments these responses showed a rate dependency In Fig 9 markedly aberrant action potential responses are shown However conduction to the normal epicardium occurs only when the action potentials at the site of stimulation [illegible] an amplitude and duration greater than the abortive (spike) potentials (Fig 8 *panel C*) This would indicate that severely disturbed cells with[illegible] abnormal zone are involved in the spread of [illegible] activation within this area and to the [illegible] zone and are not infarcted cells with no [illegible] capacities. Fig 9 also illustrates that [illegible] rate was increased further the responses of such cells deteriorated faster and often became difficult to distinguish from a stimulus artifact The latter is a passive membrane response to the applied stimulus (Fig 9 *panel A* fifth stimulu[illegible] *panel B* second and fourth stimuli) H[illegible] increasing degrees of membrane resp[illegible] seen at slower rates (abortive action po[illegible] Fig 8 *panel C*) and intermittently [illegible] rates (Fig 9 *panel C*) These observa[illegible] may represent rate-dependent failure of excita[illegible] rather than conduction failure since increasing stimulus strength (Fig 8 A to C) did not prevent action potential diminution at the higher rates

In conclusion pacing from the subepicardium of the infarcted dog heart in the period three to ten days after coronary artery ligation provides new information regarding altered conduction refractoriness and excitability In addition to underscoring the heterogeneity of the electrical properties of the abnormal tissues, these studies have characterized these disparate properties In conjunction with unidirectional block coexistence of Wenckebach Mobitz type II and repetitive forms of block in abnormal muscle can provide possible mechanisms for the common occurrence of reentry in these tissues In addition the concurrent findings of areas of inordinately long and short refractoriness can help to explain paroxysmal ventricular arrhythmias whose onset is closely coupled (R T phenomen[illegible] [illegible] previous sinus beats as well a[illegible] those init[illegible] by late coupled ectopic beats.

Summary

Reentrant ventricular arrhythmias arise [illegible] variable epicardium overlying the "transm[illegible] infarction zone in the dog 3 to 9 days after [illegible] anterior descending coronary artery [illegible] Effects of pacing (90 to 360 beats/minute) fr[illegible] the epicardium in the normal zone and ischem[illegible] zone were studied in 18 dogs using standard ECG leads and epicardial recordings. Pacing in the normal zone at any stimulus strength showed [illegible] changes in QRS morphology at these heart rates During pacing at ischemic zone sites, QRS mor[illegible]phology changed with heart rate in associati[illegible] with conduction delays in the ischemic zone Th[illegible] effect could be reversed by increasing the stimu[illegible]lus strength. Refractoriness in the ischemic zo[illegible] was tested by programmed pacing Abnormall[illegible] short (≤ 130 msec) and long (≥ 330 msec) refractoriness coexisted within the ischemic zo[illegible] This marked dispersion of refractoriness w[illegible] related to the occurrence of reentrant ventricul[illegible] arrhythmia In 10 dogs a 3 × 4 cm section [illegible] ventricular epicardium was removed wh[illegible] included normal and ischemic zones. Act[illegible] potentials were recorded during superfusion w[illegible] Tyrode s solution at 37° C Rate-dependent ree[illegible]trant ventricular arrhythmias were initiated [illegible] 90% of the tissue studied At a constant stimul[illegible] strength action potential recorded close to th[illegible] stimulation site showed progressively short[illegible] (< 100 msec.) diminutive responses as the hea[illegible] rate was increased. Intermittent failure of exci[illegible] tion was noted at higher rates. Rate-sen[illegible] changes in conduction refractoriness, and exci[illegible]tion are determinants of reentrant ventricul[illegible] arrhythmia originating in the ischemic zone ep[illegible]cardium

REFERENCES

1. Han, J Ventricular vulnerability during acute corona[illegible] occlusion, Am. J Cardiol. 24 857 1969
2. Scherlag, B. J., Helfant R. H Haft J I and Damato [illegible] Electrophysiology underlying ventricular arrhyth[illegible]mias due to coronary ligation Am J Physiol 219 [illegible] 1970
3. Durrer D., Van Dam, R. T H Freud, C E., and Ja[illegible] M J Re-entry and ventricular arrhythmias in [illegible] ischemia and infarction of the intact dog heart. P[illegible] Kon Nedrl. Akad. Van Wetensch Amsterdam [illegible] 73:321 1971
4. Boineau, J P and Cox, J L [illegible] ventricular activatio[illegible] in acute myocardial infarction A source of reentr[illegible] premature contractions. Circulation 48 70[illegible] 1973
5. Scherlag, B J El-Sherif N Hope R R and La[illegible] R. Characterization and localization of ventric[illegible] arrhythmias due to myocardial ischemia and i[illegible] Circ Res. 35:372, 1974

6 Hope R R, Williams, D O El-Sherif N Lazzara R, and Scherlag B J The efficacy of antiarrhythymic agents during acute myocardial ischemia and the role of heart rate Circulation 50 507 1974
7 Hope R R, Scherlag B J Lazzara R and El Sherif N Ventricular arrhythmias in healing myocardial infarction Role of rhythm versus rate in reentrant activation J Thorac Cardiovasc Surg 75 458 1978
8 Durrer D, VanLier A A W and Buller J Epicardial and intramural excitation in chronic myocardial infarction AM HEART J 68 765 1964
9 Elharrar V, Foster P R, Jirak T L Gaum W E, and Zipes D P Alterations in canine myocardial excitability during ischemia Circ Res 40 98 1977
10 El-Sherif N Scherlag B J, Lazzara R and Hope R R. Reentrant ventricular arrhythmias in the late myocardial infarction period I Conduction characteristics in the infarction zone Circulation 55 686 1977
11 El-Sherif N Hope R R Scherlag B J and Lazzara R. Reentrant ventricular arrhythmias in the late myocardial infarction period II Patterns of initiation and termination of reentry Circulation 55 702 1977
12 El-Sherif N Lazzara R Hope R R and Scherlag B J Reentrant ventricular arrhythmias in the late myocardial infarction period III Manifest and concealed extrasystolic grouping Circulation 56 225 1977
13 Hope R R Scherlag B J El Sherif N and Lazzara R. Continuous concealed ventricular arrhythmias, Am J Cardiol. 40 733 1977
14 Scherlag B J Abelleira J L and Samet P Electrode catheter recordings from the His bundle and the left bundle in the intact dog *in* Research in Physiology ed Kao F F, Koizumi, K., and Vassalle M., eds. Bologna 1971 Aulo Gaggi Editore p 233
15 Lazzara, R Scherlag B J Robinson M J and Samet P Selective in situ parasympathetic control of the canine sinoatrial and atrioventricular nodes, Circ Res 32:393 1973
16 Lazzara R., El Sherif N and Scherlag B J Electrophysiological properties of canine Purkinje cells in 1 day-old myocardial infarction Circ Res. 33 722 1973
17 Hope R R., Scherlag B J., and Lazzara R The induction of ventricular arrhythmias in acute myocardial infarction by atrial pacing with long short cycle sequences Chest 71 651 1977
18 Mayer A. G Rhythmical pulsation in Scyphomedusae II *in* Papers from the Tortugas Laboratory Carnegie Institution of Washington I 113 1908
19 Schmitt, F O and Erlanger J Directional differences in the conduction of the impulse through heart muscle and their possible relation to extrasystolic and fibrillary contraction. Am J Physiol. 87 326 1928 1929
20 Moe G K Evidence for reentry as a mechanism of cardiac arrhythmias Rev Physiol Biochem Pharmacol 72 55 1975
21 Wit A L Hoffman B F and Cranfield P F Slow conduction and reentry in the ventricular conducting system I Return extrasystole in canine Purkinje fibers Circ Res 30 1 1972
22 Wit A. L, Cranefield P F and Hoffman B F Slow conduction and reentry in the ventricular conducting system II Single and sustained circus movement in networks of canine and bovine Purkinje fibers Circ Res 30 11 1972
23 Anderson G J., Greenspan K., Bandura J P., and Fisch C Asynchrony of conduction within the canine specialized Purkinje fiber system Circ Res. 27 691 1970
24 Waldo A L, and Kaiser G A A study of ventricular arrhythmias associated with acute myocardial infarction in the canine heart Circulation 47 1222 1973
25 Harris A S and Rojas, A G The initiation of ventricular fibrillation due to coronary occlusion Exptl Med. Surg 1 105 1943
26 Williams, D O, Scherlag B J., Hope R R El Sherif N and Lazzara R. The pathophysiology of malignant ventricular arrhythmias during acute myocardial ischemia Circulation 50 1163 1974
27 Lazzara R El Sherif N and Scherlag B J Early and late effects of coronary artery occlusion on canine Purkinje fibers, Circ Res 35 391 1974
28 Ashman, R and Hull E Essentials of Electrocardiography New York 1945 MacMillan Publishing Co., Inc
29 Cranefield P F The Conduction of the Cardiac Impulse New York 1975 Futura Publishing Co p 15
30 Lister J W Stein F Kosowsky B D Lau S H., and Damato A N Atrioventricular conduction in man. Effect of rate exercise isoproterenol and atropine on the PR interval, Am J Cardiol. 16 516 1965
31 Lazzara R El-Sherif N Vallone T., and Scherlag B J Conduction in depressed cardiac muscle (Abstr) Circulation (Suppl 2) II 206 1975
32 DeSoyza N Bissett J J., Kane J J., Murphy M L., and Doherty J E Ectopic ventricular prematurity and its relationship to ventricular tachycardia in acute myocardial infarction in man, Circulation 50 529 1974
33 Lie K I, Wellens, H J J., Downar E and Durrer D Observations on patients with primary ventricular fibrillation complicating acute myocardial infarction Circulation 52 755 1975
34 El Sherif N Myerburg R J Scherlag B J Befeler B., Aranda, J M Castellanos, A., and Lazzara R Electrocardiographic characteristics of primary ventricular fibrillation Value of the R-on T phenomenon Br Heart J 38 415 1976
35 Rothfeld E. L., Parsonnet J., McGorman W and Linden, S Harbingers of paroxysmal ventricular tachycardia in acute myocardial infarction Chest 71 142 1977
36 Smirk, F H., and Palmer D A. A myocardial syndrome With particular reference to the occurrence of sudden death and of premature systoles interrupting antecedant T waves, Am J Cardiol. 6 620 1960
37 Hinkle L E Argyros D C., Hayes, J C., Robinson T and Alonso D R Pathogenesis of an unexpected sudden death Role of early cycle ventricular premature contractions Am. J Cardiol. 39 873 1977
38 Han J and Moe G K Nonuniform recovery of excitability in ventricular muscle Circ Res. 14 44 1964
39 Levites R., Banka V S and Helfant R H Electrophysiologic effects of coronary occlusion and reperfusion. Observations of dispersion of refractoriness and ventricular automaticity Circulation 52 760 1975

Ajmaline in WPW syndrome an electrophysiologic study

Mohammad Khalilullah M D D M (Cardiol) F C C P
Immaneni Sathyamurthy M D
Narendra K Singhal M D
New Delhi India

Ajmaline was first isolated as an alkaloid of Rauwolfia Serpentina The first report on ajmaline came from Siddiqui and Siddiqui in 1932[1] This alkaloid has no sedative hypnotic tranquilizing or hypotensive effect of Rauwolfia Serpentina Utility of ajmaline as a potent antiarrhythmic agent was reported first by Arora and Madan This was further confirmed by reports of others[3] It has been found to be particularly useful in the management of tachyarrhythmias associated with the Wolff Parkinson White (WPW) syndrome However there are very few reports on the electrophysiologic effect of this drug But the electrophysiologic effect of ajmaline in the WPW syndrome was reported by Wellens and Durrer in a study of four patients This study was planned to analyze and evaluate the qualitative and quantitative electrophysiologic changes produced by intravenous administration of ajmaline in patients with the WPW syndrome using the technique of His bundle electrography

Material and methods

Six patients three males and three females in the age range of 24 to 50 years with a mean age of 39 years formed the material of the study Three patients had type A and three had type B WPW syndrome in the basal 12 lead electrocardiogram All patients were symptomatic with recurrent tachyarrhythmias and were referred to this department for detailed electrophysiologic evaluation One of them had a recent episode of cardiac arrest All patients had the details of the study explained to them and informed consent was obtained All drugs were stopped for at least 10 days before the study which was conducted in the non sedated postabsorptive state His bundle studies were performed as per the technique established in this laboratory the details of which have been reported elsewhere In short a bipolar pacing catheter was introduced percutaneously from the femoral vein using a Seldinger needle and its tip was placed across the tricuspid valve Two more catheters were introduced from the antecubital vein for right atrial/right ventricular pacing and for recording a unipolar intra atrial (high RA) electrogram (IAE) Two or more surface leads with IAE and His bundle electrogram (HBE) were recorded on an 8 channel photorecording system Electronics for Medicine DR8 recorder using standard frequency band width Records were obtained at a paper speed of 100 mm and 200 mm per second with time lines set at 1 second intervals After the basal 12 lead scalar ECG was recorded the control electrophysiologic parameters were obtained in all patients Rapid atrial and ventricular pacing was done using a KM cardiac pacemaker/overdrive pacemaker with a pulse width of 1 msec These studies confirmed the usual electrophysiologic characteristics of the WPW syndrome Fifty milligrams of ajmaline was injected intravenously over a 10 second period and records were obtained at 30 seconds 1 minute through 15 minutes at the interval of 1 to 2 minutes and at 20 25 30 45 and 60 minute intervals in patients who showed persistent electrocardiographic and

From the Department of Cardiol g nd th) ar Laboratory G B Pant Hospital, New Delhi I d

Received f r publication May
Accepted for publication May 23

Reprint requests Dr M Khalilull h Asso Cardiology G B Pant Hospital, New Delhi 110

Table I

Patient initials	PR interval		PA		AH		HV		QRS	
	Before	After	Before	After	Before	After	Before	After	Before	After
Z.	90	1 0	10	10	90	110	−10	+50	90	90
C.L.	90	190	30	35	70	85	−10	+70	140	80
A.N	100	110	0	0	100	100	0	+10	110	70
R R	105	140	25	20	60	80	−10	+40	115	80
P.J	80	180	15	20	80	105	−15	+55	120	80
J.S	130	200	20	30	110	120	0	+50	110	90
Mean	99 16	165 0	16.7	19 1	90	100	−7.5	+4 8	119 16	81 6
P value	P 0 01		P 0 05		P 0 01		P 0 01		P 0 02	
Significance	highly significant		not significant		highly significant		highly significant		significant	

All values in msec.

electrophysiologic alterations produced by ajmaline In addition in three patients two with narrow QRS and one with broad QRS tachycardia the drug was given during the arrhythmia while continuous records were obtained Blood pressure was also recorded to detect any hypotension During complete blockade of the bypass pathway when a normal QRS interval was restored a 12 lead scalar ECG was recorded for comparative studies All resuscitative measures were kept in a standby condition

Results

All six patients studied had manifest ECG evidence of bundle of Kent operation (Type A in three and type B in three) during sinus rhythm Electrophysiological features were consistent with WPW preexcitation and pseudo WPW presentation due to simultaneous James and Mahaim preexcitation was ruled out

The details of electrophysiological effects of ajmaline are summarized in Table I No significant change in sinus rate was encountered following ajmaline administration PR prolongation was common to all with mean PR interval rising from 99 16 to 166 9 msec (Fig 1) In none did the PR interval increase beyond the normal range and the range of increase was from 10 to 100 msec Mean PJ interval demonstrated an increase from 210 msec. to 238 msec after ajmaline Mean QRS duration showed a decrease from 119 16 msec to 81 6 msec (Fig 2)

There was no appreciable alteration of the PA interval and the AH interval was only marginally affected mean AH rising from 90 msec to 100 msec (Fig 3) These effects of ajmaline lasted for 15 20 30 40 and 60 minutes in the patients studied

The most striking electrophysiologic observation was HV prolongation following ajmaline administration implying resumption of normal AV nodal His conduction (Figs 4 5 and 6) The increase in HV interval ranged from 10 to 80 msec with the mean HV interval rising from −7.5 msec before the drug to +45 8 msec after it (Fig 4) The effect on the HV interval appeared within 30 to 60 seconds of administration of the drug and persisted for 15 to 60 minutes.

Rapid atrial and ventricular pacing following ajmaline confirmed complete blockade of anomalous pathways in four patients Atrial pacing produced progressive lengthening of AH interval till AH Wenckebach block occurred with the HV interval remaining unaltered Ventriculoatrial conduction which could be elicited in all subjects before giving ajmaline was abolished following the drug

In three patients in whom tachycardia could be induced (broad QRS in one and narrow QRS in two) intravenous ajmaline was successful in restoring them to sinus rhythm within 15 seconds of administration (Figs 7 and 8) Tachycardia could not be induced in any after ajmaline had been given

Discussion

Even though nearly half a century has elapsed since its discovery yet the antiarrhythmic electrophysiologic effects of ajmaline have not yet been precisely defined While reporting their results in experimental animals Obayashi and associates observed that any effects on conduc

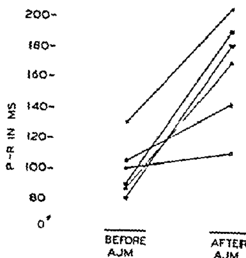


Fig 1 PR interval in six patients with WPW syndrome before and after ajmaline administration

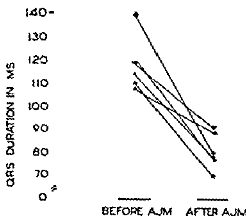


Fig 2 This graph shows the decrease in QRS duration produced by intravenous ajmaline

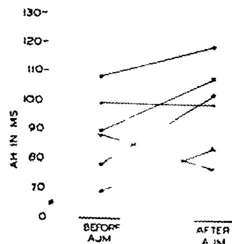


Fig 3 This graph shows th [illegible] ajmaline administration on the AH int [illegible] ith WPW syndrome In four patients the [illegible] se in AV nodal conduction time this wa [illegible] cent and shows a marginal decrease in on [illegible]

tion intervals were forthcoming only if the drug was administered in high dosages

Ajmaline has been shown to impair conduction and to cause block in the bypass pathway in patients with WPW Wellens and Durrer[4] found that of four patients with WPW three developed temporary complete blockade of the accessory pathway (AP) and the fourth patient showed a marked increase in the refractory period of AP As a result of this normalization of the QRS interval occurred with abolition of the delta wave a d restoration of normal ventricular depolarization. There is a prolongation of the HV interval without a concordant increase of the AH interval. If given during tachycardia the same can be abolished though junctional tachycardias have been reported even after normalization of the QRS interval following ajmaline Wellens and Durrer[4] also reported loss of ability to initiate tachycardias by single stimulus following ajmaline an increase in the refractory period of atrium and ventricle and increased VA conduction time following ajmaline These effects of the drug have been reported to last from 15 to 45 minutes

Ajmaline has been found to shorten the action potential duration and refractory period in normal Purkinje fibres Obayashi and colleagues observed that the main mechanism was suppression of intraventricular conduction and therefore the drug was effective in reentrant tachycardias. Chiale and co workers' have concluded that the anomalous bundle is inherently diseased and allows ajmaline to block conduction through it Their studies showed that in the dosage used (70 mg in a single intravenous injection) ajmaline did not cause bundle branch block in normal subjects whereas such block could readily be elicited when the bundle branch system was previously diseased They pointed out that ajmaline specifically causes prolongation of the ranges of phase 3 and phase 4 block both at the expense of the intermediate normal conduction range

In the present study all patients who showed WPW pattern in sinus rhythm showed quick reversion to normal AV nodal His conduction Complete blockade of the accessory pathway has been reported by Wellens and Durrer[4] and also by Puech and colleagues[11] HBE findings were consistent with the change in conduction pattern i e prolongation of the HV interval On three occasions narrow and broad tachycardias were successfully abolished with ajmaline adminis tra

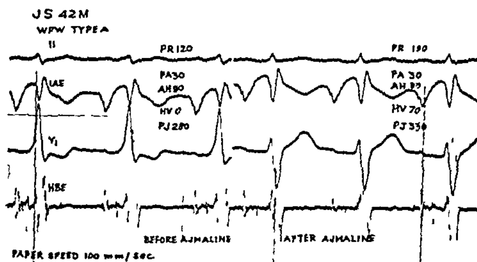


Fig 4 Basal electrophysiological parameters in a patient with type "A" WPW syndrome before ajmaline (*left side panel*) *IAE* represents high RA intra atrial electrogram *HBE* represents His bundle electrogram. A PR interval of 120 msec may suggest first-degree block at the bypass pathway After ajmaline (*right side panel*) there is a total change in ECG Lead V with abolition of the delta wave and an HV interval increasing to 70 msec from a basal of 0

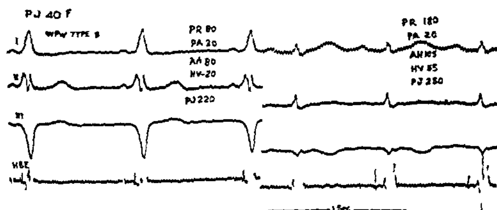


Fig 5 ECG Leads I II III and His bundle electrogram of a patient of WPW syndrome type "B" during basal condition (*left side panel*), an HV interval of −20 msec is changed to +55 msec after ajmaline This is due to normalization of AVN His conduction system with blockade of the bypass pathway This is also reflected in the increase in PR interval and decrease in QRS duration after ajmaline

tion Similar effects were observed by Homola and Smova [9] Spontaneous tachycardias following ajmaline as reported by others were not encountered in any patients and we were also unable to induce tachycardia by atrial or ventricular pacing after ajmalization VA conduction which was present in all patients was universally abolished following the drug though Wellens and Durrer[6] could elicit VA conduction in one patient following ajmaline with prolonged VA time That ajmaline has no appreciable effect on AH has also been pointed out by others

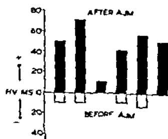


Fig 6 Bar diagram showing basal HV and HV intervals after ajmaline administration in six patients with WPW syndrome

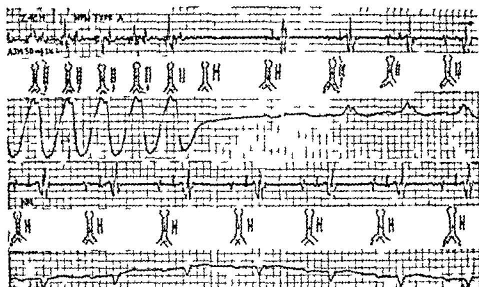


Fig 7 Continuous tracing depicting HBE and Lead V during broad QRS tachycardia at a rate of ??0/minute indicating antegrade conduction through the bypass pathway as shown by the absence of His deflection preceding V potential and retrograde conduction via the AV node as confirmed by retrograde His deflection The tachycardia is terminated by ajmaline by abolishing AV conduction along the bypass pathway as shown by the last A deflection This is not followed by a V potential The first beat following cessation of tachycardia is sinus conducted with an AH interval of 60 msec and an HV interval of 40 msec The next three complexes are fusion beats with AH interval of 100 and an HV interval of + 20 msec The lower part of the continuous tracing shows all sinus beats with an AH interval of 135 msec and an HV interval of 65 msec

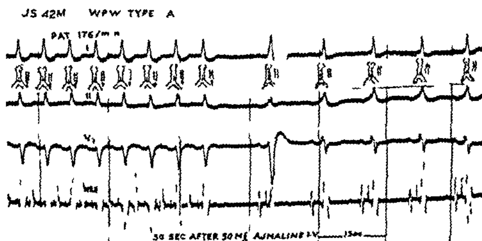


Fig 8 The tracing shows Leads I II V and HBE demonstrating narrow QRS reentrant tachycardia implying antegrade conduction through the AV node and retrograde conduction through the bypass pathway Within 30 seconds of ajmaline administration the reentrant tachycardia is abolished by blocking VA conduction due to prolongation of the refractory period of the bypass pathway The first beat following cessation of tachycardia is a sinus beat conducted with an AH interval of 100 msec and an HV interval of 30 msec with depressed intraventricular conduction a ... wide QRS The subsequent complexes show fusion beats with the same AH and HV intervals (Paper speed ... mm sec)

One shortcoming of ajmaline h... its short duration of action which in ... ranged from 15 to 60 minute ... and 60 minutes) In a similar ... and Durrer* the effect of ajmaline ... 45 minutes. However Chiale ... r

observed that the intensity and duration of the effects of ajmaline were more marked if the conduction system was already diseased (an effect lasting from several hours to 1 to 2 days) The effectiveness of ajmaline in WPW they contend may be due to a diseased state of the

anomalous bundle Two of our patients have been free of paroxymal tachycardias for the past 6 months while on oral ajmaline in the dose range of 150 to 300 mg /day

Summary

Six patients including three females with WPW syndrome (three with type A and three with type B) presenting with recurrent paroxysmal tachy arrhythmia were subject to electrophysiological studies Apart from basal parameters rapid atrial and ventricular pacing was done which confirmed electrophysiological characteristics of bundle of Kent operation A single intravenous bolus of ajmaline 50 mg was effective in blocking the bundle of Kent in all patients within 30 seconds of injection with the effect persisting for 15 minutes in one and from 25 to 60 minutes in the others The most dramatic effect was prolongation of the HV interval with normalization of QRS complex with a marginal effect on the AH interval The drug was also effective in breaking narrow QRS tachycardia in two patients and broad QRS tachycardia in one patient Long term oral thera py with ajmaline has proved effective in prevent ing recurrent tachyarrhythmias

We conclude that ajmaline is specifically effec tive and safe in the treatment of the WPW syndrome

REFERENCES

1 Siddiqui, S and Siddiqui, R H The alkaloid of Rauwol fia serpentina benth. Part I J Indian Chem Soc 9 539 1932

2 Arora R B and Madan B R Antiarrhythmics VI Ajmaline and serpentine in experimental cardiac arrhythmias J Pharmacol Exp Ther 117 62 1956

3 Dick H L H, and McCawley E L Clinical pharmaco logic observations in the effects of ajmaline in chronic atrial fibrillation Clin Pharmacol Ther 4 315 1963

4 Bazika V Lang T W Pappelbaum S et al Ajmaline a Rauwolfia alkaloid for treatment of digitotoxic ar rhythmias, Am J Cardiol. 17 227 1966

5 Lampertico M Valutazione della terapia ajmalinica in 187 patients Minerva Med 62 179 1971

6 Wellens, H J J, and Durrer D Effect of procainamide quinidine and ajmaline in the Wolff Parkinson White syndrome Circulation 50 114 1974

7 Tronoconi L L impiego dell ajmalina per via venosa e della procainemide nel tratlamento della sindrome di Wolff Parkinson White Minerva Cardioangiol. 14 2 8 1966

8 Obaya hi K Nagasawa K, Mandel W J Vyden J K, and Parmley W W Cardiovascular effects of ajmaline Am Heart J 92 487 1976

9 Wellens, H J J Effect of drugs in Wolff Parkinson White syndrome Adv Cardiol. Vol. 14 S Karger Basel 1975 p 233

10 Homola D and Smova V Anomalous atrioventricular conduction and their features Adv Cardiol Vol 16 S Karger Basel 1976 p 540

11 Khalilullah M Venkitachalam C G Mahapatra N K Pais P and Padmavati S His bundle electro gram in the disorders of conduction and impulse forma tion Indian Heart J 30 29 1978

12 Chiale P A Przybylski J Halpern M S Lazzari J O Elizari M V, and Rosenbaum, M B Comparative effects of ajmaline/on intermittent bundle branch block and the Wolff Parkinson White syndrome Am J Cardiol 39 651 1977

13 Puech P, Latour H Hertault J and Grolleau R L ajmaline injectable dans les tachycardies Paroxysti ques et le syndrome de WPW Comparison avec la procainamide Arch. Mal. Coeur 2 897 1964

Submaximal exercise testing after unstable angina*

J V Nixon M D
M C Hillert M D**
William Shapiro M D
Thomas C Smitherman M D
Dallas Texas

Data obtained in the last few years have shown that the risk of death or myocardial infarction after unstable angina is lower than had been previously suspected[1,2] Nevertheless for several months after an episode of unstable angina the risk of fatal or morbid events is higher than during stable angina pectoris About one third of patients with unstable angina later develop intractable angina pectoris or have recurrent unstable angina While some clinical features are associated with a poor outcome for these patients in general attempts to accurately predict death and myocardial infarction for individual patients with unstable angina have proved unsuccessful[2] Furthermore little information is available regarding the prediction of patients who subsequently develop severe stable angina pectoris or recurrence of their unstable angina

While several reports have suggested that unstable angina constitutes an acute emergency requiring prompt cardiac catheterization and bypass surgery for optimal therapeutic results randomized controlled trials have not supported this view In the light of the risks and costs accompanying cardiac catheterization and coronary artery bypass surgery the evaluation of any noninvasive procedure that may assist the clinician in the management of the individual patient with unstable angina appears warranted

The value of the exercise test in the diagnosis and functional evaluation of the patient with stable angina pectoris is well established[10] Recent reports have demonstrated the value of exercise testing after acute myocardial infarction[11] Similar studies have not been reported in patients following unstable angina This study was carried out in patients with unstable angina to determine (1) whether submaximal exercise testing prior to hospital discharge is a safe procedure and (2) if the exercise test may be useful in the identification of those patients likely to experience further events of myocardial ischemia soon after hospital discharge

Materials and methods

Patient selection Unstable angina was defined as worsening of previous angina pectoris or the new onset of progressive angina pectoris within four weeks prior to presentation to the hospital A diagnosis of ischemic heart disease was required and established by one or more of the following criteria (1) previous documented myocardial infarction (2) electrocardiographic evidence of myocardial ischemia (> 1 mm of horizontal or downsloping ST segment depression sustained for 0 08 sec beyond the J point) (3) previous positive maximal exercise test (4) documented disease by coronary arteriography or (5) a previous history of typical angina pectoris Patients with possible precipitating events or concurrent disease were

From the Cardiovascular Serv[illegible] Veteran Administration Medical Center and the Department [illegible] Internal Medicine [illegible] Southwestern Medical School, Un[illegible] of Texas Health [illegible] Center Dallas, Texas.

Received for public[illegible] Jul[illegible] 1979

Accepted for publication Dec[illegible] 1979

Reprint requests J V N[illegible] M D [illegible] Veterans Administration Medical C[illegible] 4500 S Lan[illegible] Texas 75216

Presented in part at the An[illegible] American Heart Association, Dallas, Tex[illegible] November

This study was carried out dur[illegible] postdoctoral research trainee supported [illegible]

0002-8703/80/060772 + 07$00 70/0 © 1980 The C V Mosby Co

excluded Patients who developed an acute myocardial infarction were also excluded Acute myocardial infarction was documented by diagnostic QRS changes and/or ST segment and T wave abnormalities on the electrocardiogram consistent with myocardial ischemia associated with elevation of any two of the three cardiac enzymes (creatine kinase glutamic oxaloacetic transaminase or lactic dehydrogenase) to at least twice the upper limits of normal Only patients fulfilling these above criteria and who responded to medical therapy were considered for study Response to medical therapy was adequate if the patient was pain free or returned to the previous pattern of chronic stable angina pectoris during his hospitalization

Sixty one consecutive male patients ages ranging from 42 to 70 years and mean age 56 years admitted to the coronary care unit were studied Forty two of the 61 patients were receiving oral propranolol therapy at the time of the submaximal exercise test Each test was performed a few days prior to discharge and at least 3 days and usually one week after their last episode of angina Informed consent was obtained from each patient The test was supervised by a physician and a specially trained technician

Follow up data were available on 55 patients over a period of 6 to 36 weeks (mean 18 weeks) after hospital discharge Exercise tests symptom limited or targeted to 90% of the patients predicted maximal heart rate were obtained on 31 patients within 20 weeks (mean 10 weeks) of hospital discharge

Exercise testing Exercise was performed on a Monark bicycle ergometer The electrocardiogram was continuously monitored on a Hewlett Packard 1516A tape terminal attached to a Hewlett Packard 1309A oscilloscope using a modification of Frank s orthogonal lead system [1] Permanent recordings at 25 mm /sec were made before exercise during the last 30 seconds of each level of exercise obtained and during the first 30 seconds of each post exercise minute of observation (5 minutes or until return to pre exercise status) Indirect blood pressure recordings were obtained at one minute intervals throughout the study by the Doppler technique using an Arteriosonde (Roche) Each patient commenced exercise at 150 kpm /minute increasing by increments of 150 kpm /minute every 3 minutes until the individual endpoint was reached

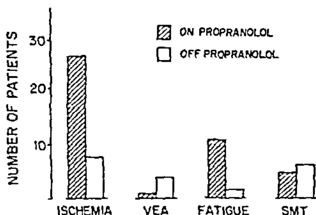


Fig 1 Numbers of patients on and off propranolol who prematurely terminated their submaximal exercise test due to chest pain and/or significant electrocardiographic changes *(ISCHEMIA)* ventricular ectopic activity *(VEA)* or fatigue or achieved the target heart rate of 120 beats/minute *(SMT)*

The submaximal exercise test was targeted to a heart rate of 120 beats per minute Indications for premature termination of exercise in our laboratory have been described elsewhere and include typical angina pectoris electrocardiographic ST segment changes of 1 mm or greater exercise hypotension and ventricular ectopic activity of Grade 2 or higher (that is more than three unifocal ventricular premature beats per minute multifocal ventricular premature beats ventricular couplets or tachycardia or the R on T phenomenon) [1 10] Otherwise if it was not prematurely terminated by patient fatigue the exercise test was discontinued at the target heart rate

Statistical analysis Data were evaluated by chi square analysis and by analysis of variance [1]

Results

The reasons for terminating the maximal exercise tests are shown in Fig 1 In no patient was recurrence of unstable angina or acute myocardial infarction precipitated by the exercise test Exercise was terminated by an evidence of myocardial ischemia (chest pain and/or significant electrocardiographic ST segment changes) in 34 patients (56%) 26 of whom were receiving propranolol Fourteen patients had electrocardiographic changes alone 10 patients had both chest pain and electrocardiographic changes and 10 patients had chest pain only Premature termination of the exercise by ventricular *ectopic activity*

Table I Hemodynamic levels at termination of submaximal exercise (mean ± SE)

	On propranolol (*n* = 42)	*Off propranolol* (*n* = 19)	*p*
Heart rate (beats/min)	99 ± 2	110 ± 4	< .01
Work load (kpm/min)	349 ± 24	234 ± 31	< .01
Heart rate × systolic blood pressure/100	141 ± 3	136 ± 4	NS

Abbreviations kpm/min = kilopond meters per minute p = probability

Table II Clinical status of 55 patients in whom follow up data were available compared to reasons for termination of pre discharge submaximal exercise

NYHA Class	*All patients*			*On propranolol*			*Not on propranolol*		
	I or II	*III*	*IV*	*I or II*	*III*	*IV*	*I or II*	*III*	*IV*
Number of patients	27	5	23	22	3	15	5	2	8
Significant electrocardiographic changes ± chest pain	8	3	17	7	1	10†	1	2	
Chest pain only	4	1	3	4	1	3	0	0	0
Fatigue	10	0	2	9	0	2	1	0	0
Achieved target heart rate	5	1	1	2	1	0	3	0	1

$p < 0.00$[illegible]
†$p < 0.05$
NYHA Class = New York Heart Association Classification

occurred in only five patients (8%) Three of the five patients had multifocal ventricular premature beats one of whom had ventricular couplets and two patients had unifocal ventricular premature beats at greater than 3 per minute Only one of these five patients was on propranolol therapy Thirteen patients (21%) spontaneously terminated their tests because of leg fatigue 11 of these were receiving propranolol Only nine patients reached their target heart rate of 120 beats/minute four of whom were on propranolol therapy

The mean values of heart rate work load and double product (heart rate × systolic blood pressure/100) at the termination of exercise are shown in Table I In patients on propranolol mean peak heart rate (99 [illegible] beats/minute $p < 0.01$) was lower and mean threshold work load (349 ± 24 kpm minute p [illegible] 0.01) was higher than those off propranolol (heart rate 110 ± 4 beats/minute work load 23[illegible] kpm/minute) Mean values for double pr[illegible] similar in both groups

The clinical status [illegible] whom follow up data were available [illegible] divided into three groups Twenty seven [illegible] d no further chest pain or only mild angina pectoris (NYHA Class I and II) Five patients had further episodes of severe but stable angina pectoris (NYHA Class III) Twenty three patients had further episodes of unstable angina and/or intractable angina pectoris (NYHA Class IV) The reasons for termination of the submaximal exercise tests in these patients are shown in Table II Forty patients were receiving propranolol therapy at the time of their exercise test Of 23 patients with NYHA Class IV angina 17 patients (74%) had the exercise tests prematurely terminated by significant electrocardiographic changes (either significant ST segment changes or ventricular ectopic activity) with or without associated chest pain ($p < 0.005$) This significant finding persisted in Class IV angina patients receiving propranolol 10 of 15 patients (67%) on propranolol had significant exercise induced electrocardiographic changes ($p < 0.05$) Eight patients (30%) with NYHA Class I and II angina and three patients (60%) with NYHA Class III angina had their exercise tests prematurely terminated by electrocardiographic changes

Thirty one patients had maximal stress tests performed within 20 weeks of hospital discharge

Table III Response to symptom limited exercise in patients who had both pre discharge and post discharge studies (Mean ± SE)

Time of test	Number of patients	Heart rate (beats/min.)	Work load (kpm /min)	Systolic BP (mm Hg)	RPP	Evidence of ischemia
Pre-discharge (submaximal)						
All patients	28	98 ± 2	310 ± 24	142 ± 3	136 ± 4	20(71%)
On propranolol	20	95 ± 3	335 ± 29	143 ± 4	132 ± 4	13
Not on propranolol	8	104 ± 5	246 ± 40	140 ± 4	145 ± 8	7
Post-discharge (maximal)						
All patients	28	104 ± 4	[illegible]97 ± 25	141 ± 3	147 ± 7	18(64%)
On propranolol	25	103 ± 4	306 ± 36	143 ± 3	148 ± 8	15
Not on propranolol	3	113 ± 6	2[illegible]5 ± [illegible]5	128 ± 9	144 ± 11	3

Chest pain a d/or significant electrocardiographic changes
Abbreviations kpm./min. = kilopond meters/minut BP = bl od pressure RPP = rate-pressure product (heart rate × systolic blood pressure/100)

Table IV Response to exercise at constant workloads of 150 kpm /min in 24 patients and 300 kpm /min in 15 patients (mean ± SE)

Workload (kpm /min.)	Time of test	Heart rate (beats/min.)	Systolic BP (mm Hg)	RPP	Evidence of ischemia
150	Predischarge (submaximal)	87 ± [illegible]	12[illegible] ± 2	110 ± 3	2 (8%)
	Postdischarge (maximal)	86 ± 3	1[illegible]9 ± 3	113 ± 4	1 (4%)
300	Predischarge (submaximal)	95 ± 3	141 ± 3	134 ± 4	5 (33%)
	Postdischarge (maximal)	104 ±	141 ± 3	147 ± 9	3 ([illegible]0%)

Chest pain and/or significant electrocardiographic changes at given workload
Abbre iations BP = blood pressure kpm /min. = kilopo d meters per min t
RPP = rate pressure product (h art rate × systolic blood pressure/100)

Three of these patients reached the target heart rate of 120 beats per minute during their pre discharge submaximal exercise tests Compara tive exercise data for the remaining 28 patients who had symptom limited pre-discharge and post-discharge tests are shown in Table III No significant changes occurred in threshold heart rate work load systolic blood pressure or rate pressure product in all patients or when patients on and off propranolol were considered separate ly Furthermore the number of patients with evidence of exercise induced myocardial ischemia (significant ST segment changes and/or chest pain) did not change significantly between pre discharge submaximal and post discharge maxi mal studies Of the 20 patients (71%) who had ischemic responses during their pre discharge studies, 16 had similar responses during their post discharge study two patients who had pre maturely stopped with fatigue in their first study subsequently had their post discharge study pre maturely terminated by an ischemic response Twenty patients were receiving propranolol at the time of their pre discharge test and five additional patients were receiving the drug at the time of their post discharge maximal test

The serial response to exercise at constant workloads of 150 kpm /minute in 24 patients and 300 kpm /minute in 15 patients is shown in Table IV The remaining patients failed to achieve these workloads during either their pre discharge or post discharge exercise tests No significant changes at either workload occurred in heart rate systolic blood pressure or rate pressure product The incidence of exercise induced myocardial ischemia at each given workload was lower in the post discharge studies but the reduction was not significant

Discussion

The risks of exercise testing in patients with stable angina pectoris have been previously reported.[19] The roles of submaximal and maximal exercise testing following acute myocardial infarction have been studied in several centers recently and were demonstrated to be of value in the assessment of functional capacity and the suitability of rehabilitation in these patients.[14,15] No similar data are known to us, however, regarding patients following unstable angina. While the numbers of patients are too few to permit precise conclusions, the results of this study suggest that under the strict criteria incorporated in our study protocol, submaximal exercise testing soon after unstable angina is not a hazardous procedure.

While several clinical features have been implicated as predictors of death or myocardial infarction following unstable angina, predictors of the severity of subsequent angina have not been extensively sought out.[1,3,13,5] It has been reported that as many as one third of patients with unstable angina develop subsequent episodes of unstable angina or intractable angina pectoris. While not dealing with death or myocardial infarction, the results of our present study suggest that submaximal exercise testing provides useful prognostic information regarding subsequent angina in patients who stabilize on medical therapy. The occurrence of exercise induced electrocardiographic changes on the submaximal exercise test appears to predict an unfavorable clinical course after hospital discharge and may thus be of aid in selecting patients for early coronary artery bypass surgery.

The role of coronary artery surgery after unstable angina remains controversial. Randomized controlled prospective trials have shown that surgical intervention soon after unstable angina is effective in decreasing the frequency and severity of angina but does not reduce the incidence of death and appears to increase the risk of myocardial infarction. Because of these findings it has been suggested that patients with unstable angina should be stabilized with medical therapy if possible, deferring a decision regarding surgical therapy until the severity of the [illegible] subsequent angina has been established. On the other hand, it has been shown that despite [illegible] tantial costs of bypass surgery, the [illegible] sent hospitalization of patients who ha[illegible] rent unstable angina or intractable [illegible] and receive only medical therapy may equal or even exceed the costs of surgery.[20] Thus, a method of predicting the subsequent severity of angina in these patients after hospital discharge may help to resolve the dilemma of management of patients who stabilize on medical therapy after unstable angina.

Four of the five patients whose tests were terminated because of exercise induced ventricular ectopic activity were not receiving propranolol therapy. Propranolol has been shown in our laboratory to reduce the frequency of exercise induced ventricular ectopic activity in patients with chronic ischemic heart disease, and in particular the high grades of ventricular ectopic activity.[21] Although the numbers of patients are small, precluding definitive conclusions in these patients with unstable angina, this study suggests that propranolol has a protective effect in reducing the incidence of exercise induced ventricular ectopic activity following unstable angina. Furthermore, propranolol therapy did not significantly affect the frequency of an exercise induced ischemic response in these patients. Previous studies in our laboratory have shown that while the frequency of an exercise induced ischemic response is reduced by propranolol in patients with two vessel coronary disease, it is not affected by propranolol in patients with three vessel or left main disease.[9] The data in our present study suggest that these patients with unstable angina have more severe coronary artery disease, agreeing with the previous study of Allison and colleagues[4] on similar patients.

It has been reported in patients who underwent serial exercise tests following an acute myocardial infarction that there are both early and late phases of improvement in the impaired cardiovascular function resulting from the infarction.[1] The improvement was determined by clinical and electrocardiographic estimates of the threshold of myocardial ischemia, including exercise induced chest pain or electrocardiographic changes, peak work load or peak heart rate blood pressure product. Similar analysis of serial exercise data of our patients after unstable angina showed no significant changes in clinical or electrocardiographic estimates of myocardial ischemia at either maximal symptom limited exercise or at differing constant workloads. These data suggest that should impaired cardiovascular function occur during unstable angina, any recovery in function occurs

soon after stabilization on medical therapy and before the pre discharge submaximal exercise test has been performed[38]

In conclusion the results of the present study demonstrated that submaximal exercise testing soon after unstable angina is not a hazardous procedure if the test is closely monitored and promptly terminated by well defined criteria While numbers were small propranolol appears to have a protective effect in reducing the incidence of exercise induced ventricular ectopic activity Exercise induced abnormal electrocardiographic changes in pre discharge submaximal exercise tests significantly predicted further episodes of unstable angina in a mean follow up period of 18 weeks Comparison of serial exercise data from pre discharge submaximal and post discharge maximal exercise tests suggested that any recovery in cardiovascular function after unstable angina occurs soon after stabilization and prior to the pre discharge submaximal test

Summary

Sixty one consecutive men mean age 56 years who fulfilled criteria for unstable angina and who responded to medical therapy underwent submaximal exercise testing prior to hospital discharge and at least 3 days after their last episode of angina Forty two patients were receiving propranolol at the time of exercise Submaximal exercise was targeted to 120 beats/minute and strict criteria for the premature termination of each study were followed Follow up data were available on 55 patients post discharge over a period of 6 to 36 weeks

No patient suffered recurrence of unstable angina or myocardial infarction due to the exercise test Exercise was prematurely terminated by an ischemic response (chest pain and/or ST segment changes) in 34 patients (56%) and by leg fatigue in 13 patients (21%) Only five patients had exercise induced ventricular ectopic activity four of whom were not receiving propranolol Nine patients achieved the target heart rate Exercise induced abnormal electrocardiographic changes predicted the postdischarge recurrence of episodes of unstable angina ($p < 0.05$) Comparison of predischarge submaximal exercise data with postdischarge maximal exercise shows that recovery in cardiovascular function after unstable angina occurs soon after stabilization and prior to the submaximal test

The authors wish to express their gratitude to Larry Burden R N for his administrative assistance to Janet Park and Frankie Kirkwood for their technical assistance and to Susan Moody and Lucy Pittman for their secretarial help

REFERENCES

1 Gazes P C Mobley E H Jr Faris H M Jr Duncan R C and Humphries C B Preinfarctional (unstable) angina—a prospective study—ten year follow up Circulation 48:331 1973

2 Duncan B Felton M Morrison S K Lutz W Donald K W Kirby B J Julian D G and Oliver M G Prognosis of new and worsening angina Br Med J 1 981 1976

3 Krauss K R Hutter A M Jr and DeSanctis R W Acute coronary insufficiency Arch Intern Med 129 808 1972

4 Unstable Angina Pectoris Study Group Unstable angina pectoris national cooperative study group to compare medical and surgical therapy II In hospital experiences and initial follow up results in patients with one two and three vessel disease Am J Cardiol 42 839 1978

5 Geha A S Baue A E Krone R J et al Surgical treatment of unstable angina by saphenous vein and internal mammary artery bypass grafting J Thorac Cardiovasc Surg 71 348 1976

6 Vogel R Pappas G Levitt P et al Results of medical and surgical management of high risk unstable angina (Abstr) Am J Cardiol 35 175 1975

7 Flemma R J Johnson D Tector A J et al Surgical treatment for preinfarction angina Arch Intern Med 129 878 1972

8 Selden R Neill R A Litzman W Okies J E and Anderson R P Medical versus surgical therapy for acute coronary insufficiency a randomized study N Engl J Med 293 1329 1975

9 Pugh B Platt M R Mills L J Crumbo D S Poliner L Curry G C Blomqvist C G Parkey R W Buja L M and Willerson J T Unstable angina pectoris A randomized study of patients treated medically and surgically Am J Cardiol 41 1291 1978

10 Blomqvist C G Use of exercise testing for the diagnosis and functional evaluation of patients with arteriosclerotic heart disease Circulation 44 1120 1971

11 Ericsson M Granath A Olson P Sodermark T and Volpe U Arrhythmias and symptoms during treadmill testing three weeks after myocardial infarction in 100 patients Br Heart J 35 787 1973

12 Ibsen H Kjoller E Styperek J and Pederson A Routine exercise ECG three weeks after acute myocardial infarction Acta Med Scand 198 463 1975

13 Crumbo D S Ritter W S Osborn R C Shapiro W and Smitherman T C Prediction of late ventricular ectopy following myocardial infarction (Abstr) Clin Res 25 3A, 1977

14 Markiewicz W, Houston N and DeBusk R F Exercise testing soon after myocardial infarction Circulation 56 26 1977

15 Naughton J Shanbour K Armstrong R, McCoy L, and Lategola T Cardiovascular responses to exercise following myocardial infarction Arch Intern Med 117 541 1966

16 Kentala E Physical fitness and feasibility of physical rehabilitation after myocardial infarction in men of working age Ann Clin Res 4(Suppl 9) 1 1972

17 Sanne H Exercise tolerance and physical training of nonselected patients after myocardial infarction Acta Med Scand (Suppl 551) 1 1973

18 Wohl, A J Lewis, H R Campbell W Karlsson E Willerson J T., Mullins C B and Blomqvist C G Cardiovascular function during early recovery from acute myocardial infarction Circulation 56 931 1977

19 Blomqvist C G Astrand, I and Messin R Clinican physiological and electrocardiographic findings in patients with angina pectoris during work in cold environment and during arm work Acta Med Scand 178(Suppl 440) 74 1965

20 Lown B and Wolf M Approaches to sudden death from coronary artery disease Circulation 44 130 1971

21 Zar J H *In* Biostatical Analysis Englewood Cliffs, N.J 1974 Prentice-Hall.

22 Atterhog J H., Jonsson B., and Samuelson R Exercise testing a prospective study of complication rates AM HEART J 98 572 1979

23 See J R., Cosby R S Giddings J A and Mayo M Medical management of acute coronary crises (Abstr) Circulation 46(Suppl II) 218 1972

24 Watkins P C., Russell R O Jr., and Rackley C E Follow up study of unstable angina in a myocardial infarction research unit (Abstr) Circulation 46(Suppl. II) 23 1972

25 Heng M K Norris R M., Singh, B N., and Pantridge J B Prognosis in unstable angina Br Heart J 38 921 1976

26 Kronenfeld J J Charles E D., Wayne J B Russell R O Jr., Oberman A., Kouchoukas, N Rogers, W J and Rackley C E Medical versus surgical treatment and costs of unstable angina pectoris (Abstr) Circulation 67(Suppl II) 96 1978

27 Nixon J V Pennington W Ritter W and Shapiro W Efficacy of propranolol in the control of exercise induced or augmented ventricular ectopic activity Circulation 57 115 1978

28 Nixon J V., Lipscomb K Blomqvist C G and Shapiro W Exercise testing in men with significant left main disease Br Heart J 42 410 1979

29 Allison H W., Russell R O Jr Mantle J A., Kouchoukas N T., Moraski, R E and Rackley C E Coronary anatomy and arteriography in patients with unstable angina pectoris, Am J Cardiol. 41 204 1978

30 Chatterjee K Swan H J C., Parmley W W Sustaita H. Marcus H and Matloff J Depression of left ventricular function due to acute myocardial ischemia and the reversal after aorto-coronary saphenous vein bypass N Engl. J Med 286 117 1972

Case reports

Laennec's cirrhosis and primary pulmonary hypertension*

Patrick K C Chun M D MAJ MC
Richard P San Antonio M D CPT MC
James E Davia M D COL MC F A C C
Washington D C

There have been few reports[1-4] of the rare association of cirrhosis and primary pulmonary hypertension This case report adds to the literature a well-documented case of the foregoing and also reviews the literature

Case report

The patient is a 40-year old female who was born and raised in France With each meal she consumed a half bottle of wine She was entirely well until 1968 when at age 30 she presented with a complaint of amenorrhea Physical examination revealed hepatosplenomegaly An upper gastrointestinal study demonstrated a duodenal ulcer which was managed medically In 1970 the patient had acute bleeding of the upper gastrointestinal tract After medical stabilization a liver biopsy was performed (Fig 1) It documented a marked increase in connective tissue surrounding pseudolobules with bile duct proliferation There was chronic inflammation but no definite alcoholic hyaline There was one focus of acute inflammation in the parenchyma. No pigment accumulation was present Copper stains were negative HB Ag fluorescent antinuclear antibody and serum protein electrophoresis were unremarkable This was felt to be consistent with nutritional or Laennec s cirrhosis The patient was subsequently readmitted on multiple occasions for upper gastrointestinal tract bleeding

In 197? after another episode of bleeding in the upper gastrointestinal tract endoscopy demonstrated numerous esophageal and gastric varices Peritoneoscopy revealed a prominent accessory hepatic lobe The liver surface was pale and uniformly studded with millet seed like lesions representing dilated lymphatic ductules. Neovascularization over the surface of all three lobes was noted. Coarse nodularity in addition to micronodularity was also noted on both anterior and inferior liver surfaces. A portacaval shunt was discussed but was not felt to be warranted at this time Her dyspepsia iron deficiency anemia, and trace ascites were respectively managed with antacids iron and diuretics with good results

During this admission the patient was noted to have a systolic murmur and ejection click. The patient was referred to the Cardiology Service for further evaluation. The patient denied any history of rheumatic fever effort syncope chest pains, dyspnea paroxysmal nocturnal dyspnea orthopnea cyanosis, or edema The patient has one child, a daughter who is 21 years old alive and well. The patient has smoked a half pack of cigarettes per day over the last 20 years. There was no history of diabetes hypertension use of oral contraceptives, anorectic agents, or exposure to any tropical diseases.

Physical examination revealed a jaundiced female with a cardiac examination consisting of a palpable S_4 and an increased P of the second heart sound. There was an ejection click heard best at the second right intercostal space increasing with expiration There was a systolic ejection murmur heard best at the second left intercostal space Grade II increasing with inspiration The P was equal to A There were no diastolic murmurs, gallops bruits cyanosis or edema Abdominal examination revealed a liver of 14 cm in span and a palpable spleen tip There was no ascites

The electrocardiogram (Fig 2) in 1978 demonstrated early R wave progression suggestive of right ventricular hypertrophy (RVH) with right axis deviation. The vectorcardiogram was consistent with type C RVH The echocardiogram revealed normal septal motion, a normal "a" dip in the pulmonic valve and evidence of right ventricular dilatation The chest x ray (Fig 3) demonstrated right ventricular enlargement and prominent pulmonary artery segments bilaterally

The cardiac catheterization data are recorded in Table I At cardiac catheterization severe pulmonary hypertension was found There was no gradient across the pulmonic valve Saturations on pullback revealed no step-up. Hydrogen

From the Cardiology Service Walter Reed Army Medical Center Washington, D C

Received for publication Dec. 28 1978
Accepted for publication Feb 16 1979

Reprint requests Patrick K C Chun M D Cardiology Service, Walter Reed Army Medical Center Washington D C 20012

*The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Department of the Army or the Department of Defense

Fig 1 Increased connective tissue around pseudolobules with bile duct proliferation and chronic portal infl mmati n consistent with Laennec s cirrhosis

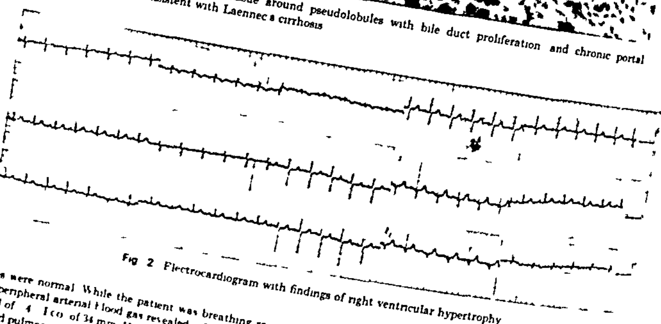


Fig 2 Electrocardiogram with findings of right ventricular hypertrophy

s were normal While the patient was breathing room peripheral arterial blood gas revealed a Po of 6" mm l of 4 I co of 34 mm Hg and So of 14 Because of d pulmonary artery pressures a pulm nary angiogram performed However a manual nject n f dye into monary artery dem nstrated n evid n e f peripheral tenosis

onal studies were performed including a elia and mesenteric arteriogram Small pun tate al th a he head of the pancrea w re r ted Il r wa ng of the hepatic vessel n licating h p w l l r

disease There was no evidence of neoplasm The splenic vein was noted to be patent The portal vein was not visualized on the superior mesenteric arteriogram The perfusion lung scan demonstrated a patchy distribution as well as a specific isolated sub-segmental defect in the upper posterior aspect of the left lung which later filled This was consistent with multiple emboli Complete pulmonary function tests revealed a mild obstructive ventilatory defect with increased residual volume A multiple gated acquisition scan revealed the left ventricle to have a decreased volume a hyperkinetic wall motion and an ejection fraction of 60"

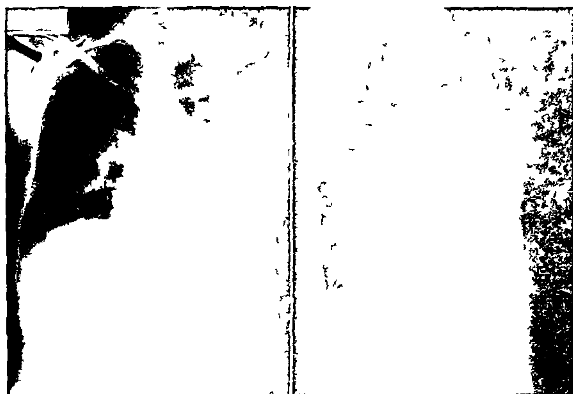


Fig 3 Chest x ray with prominent pulmonary artery segments bilaterally and RVH (posteroanterior [*left*] and lateral [*right*] films)

Discussion

There are many ways in which hepatic disease influences the general circulation Hemodynamic measurements have revealed abnormalities in patients with cirrhosis These include tachycardia reduced arterial oxygen saturation diminished cardiac output widened pulse pressures expanded blood volume reduced vascular resistance and shortened circulation time Hepatic artery oxyhemoglobin saturations have been found to be less than 94% Venous admixture from arteriovenous shunts between the portal and pulmonary circulations has been implicated as the pathophysiologic mechanism Venoarterial shunts in cirrhosis have been found to account for an average of 9 5% of the cardiac output[7] Increased cardiac output has also been observed by investigators and has been found to be associated with an increased plasma volume increased stroke volume normal peripheral blood pressure and increased hepatic vein wedge pressure This has been ascribed to decreased peripheral vascular resistance caused by dilation of the peripheral vascular bed and possible arteriovenous shunting in the extremities Cardiac hypertrophy has also been found in cirrhotic subjects and this has been thought to involve chiefly the right ventricle The exact relation of cardiac hypertrophy to increased pulmonary pressures or to increased cardiac output is not known It has also been suggested that cirrhosis is associated with a specific myocardial disease Patients with cirrhosis not only have common types of heart disease but are also prone to develop an idiopathic type of heart disease[7]

Table I Cardiac catheterization data

Site	*Systolic and diastolic pressures*	*% O saturation*
SVC	a = 10 v = 1[illegible] $\overline{10}$	74
RA	a = 10 v = 8 $\overline{5}$	7[illegible]
RV	[illegible]0/10	73
PA	70/30 $\overline{50}$	71
PAW	a = 10 v = 12 $\overline{10}$	98

More specifically our patient has the rare *association of pulmonary hypertension with cirrhosis* of the liver In previous case reports of cirrhosis and pulmonary hypertension 60% (19 of 32) of the patients had hemodynamic measurements documenting the pulmonary artery hypertension In the others pulmonary hypertension was suspected on clinical or anatomic grounds Nineteen of the 32 were subsequently documented to have pulmonary plexiform lesions at autopsy

In most instances pulmonary hypertension can be readily established by both clinical and invasive studies The underlying cause i e congenital or acquired heart disease recurrent pulmonary emboli interstitial pulmonary fibrosis pulmonary emphysema or pulmonary veno occlusive disease is usually apparent Pulmonary hypertension is then recognized as a feature of the underlying condition There is however a residuum of cases of pulmonary hypertension for which no cause is evident Such cases as exemplified by this patient are then diagnosed as having primary pulmonary hypertension

In a pathologic description of primary pulmonary hypertension Edwards and Edwards point out the difficulty of documenting pulmonary vascular lesion histologically The lesions may be extremely focal while most of the pulmonary vessels may be normal As a result the extent of the involvement of the pulmonary vasculature in any one tissue section may appear to be deceptively scant Of the three pathological patterns that they described the plexigenic type more frequently developed in the cases of hepatic cirrhosis as well as in patients ingesting various anorectic drugs and in those with schistosomiasis

The hemodynamic disturbances in hepatic cirrhosis have been attributed to idiopathic changes in the pulmonary vessels expansion of the pulmonary blood volume due to expanded total blood volume thiamine deficiency excessive activity of vasodilator material that is normally inactivated by the liver and emboli from thrombosed portal veins gaining access to the systemic venous system through enlarged collateral veins or to an immunologic mechanism as involved in chronic active hepatitis However the basic mechanism behind the association of primary pulmonary hypertension and cirrhosis has still to be supported by firm data Nevertheless the clinical association of these hemodynamic disturbances with cirrhosis is evident and should be brought to the attention of physicians

Summary

The association of cirrhosis and primary pulmonary hypertension has been rarely reported This case report adds to the literature a case documented by liver biopsy and cardiac catheterization The literature on this subject and potential pathophysiologic mechanisms of association are reviewed

REFERENCES

1 Naeye R L "Primary" pulmonary hypertension with coexisting portal hypertension Circulation 22 376 1960
2. Cohen N and Mendelow H Concurrent active juvenile cirrhosis and "primary pulmonary hypertension" Am J Med. 39 127 1965
3 Segel, N., Kay J M Bayley T J and Paton, A Pulmonary hypertension with hepatic cirrhosis Br Heart J 30 575 1968
4 Senior R M., Britton R C Turino G M Wood J A Langer G A., and Fishman A P Pulmonary hypertension associated with cirrhosis of the liver and with portacaval shunts Circulation 37 88 1968
5 Aach R., and Kissane J M A fifty-six year old woman with jaundice and pulmonary hypertension Am J Med 47:287 1969
6 Cryer P E., and Kissane J M Chronic active hepatitis and pulmonary hypertension Am J Med. 63 604 1977
7 Bockus, H L Cardiovascular Abnormalities in Cirrhosis. Gastroenterology 2nd edition Philadelphia & London 1965 W B Saunders Company Vol III 228-229 1965
8 Edwards, W D and Edwards, J E Clinical primary pulmonary hypertension Circulation 56 884 1977

Histoplasma capsulatum endocarditis*

Timothy P Blair LCDR MC USNR
Robert A Waugh CDR MC USNR*
Matthew Pollack LCDR MC USNR
Halbert E Ashworth CAPT MC USN
Nathaniel A Young M D *
Seth E Anderson CDR MC USN **
Thomas P Bem LCDR MC USNR
Bethesda Md

Nearly 40 years have passed since Humphrey described the initial case of *Histoplasma capsulatum* endocarditis Only 21 cases of this rare manifestation of histoplasmosis have been reported in the literature and only four patients have survived We report a case with aortic valve involvement which was cured by therapy with amphotericin B and aortic valve replacement

Case report

Patient W C a ?? year old white male was in excellent health until April, 1975 when he developed fatigue nocturnal fevers to 38 C and a 7 kg weight loss. In September 19 5 he was admitted to another hospital where physical examination was normal except for cardiac findings that included an aortic ejection click a Grade II/VI systolic ejection murmur radiating to the base and apex and a Grade I/VI high frequency diastolic decrescendo murmur at the left lower sternal border and the second right intercostal pace An echocardiogram revealed variably eccentric aortic valve closure and ariable hickenin of the aortic leaflets in systole and/or diastole depending on transducer angulation A sweep was not performed The findings were considered to be consistent with endocarditis and/or a bicuspid aortic valve with mild aortic regurgitation Although endocarditis was strongly considered the patient s normal hematocrit leukocyte count erythrocyte sedimentation rate absence of rheumatoid factor negative blood cultures and spontaneous defervescence prompted the patient s discharge

Fever recurred in October 1975 and on November 1 1975 he experienced sudden numbness and weakness in his left arm and leg which pontaneously resolved in one hour He was admitted on November 6 1975 for further evaluation

The patient was a native of Tennessee where he had pent most of his life There was no history of rheumatic fever or other known valvular heart disease drug misuse recent dental work or diagnostic in trumentation

Physical examination revealed a thin chronically ill appearing white male in no acute distress The blood pressure was 114 40 mm Hg the pulse 96 per minute and regular and the temperature 37 5 C orally The carotid pulse contour was normal and the left ventricular impulse was not displaced. Auscultation revealed normal first and second heart sounds a Grade II/VI systolic ejection murmur was present with maximal intensity at the second right intercostal space and radiation to the apex and carotid arteries There was a grade III/VI diastolic decrescendo murmur at the second right intercostal pace that extended to S_1 and was heard well at the right and left lower sternal borders An ejection click was heard by some observers Except for a palpable spleen tip the remainder of the physical examination was normal

The hematocrit was 39% hemoglobin 12.8 gm/dL and leukocyte count 4 ?00/mm with ?% bands 4?% polymorphonuclear leukocytes and 46% lymphocytes The erythrocyte sedimentation rate was 33 mm/hr and rheumatoid factor was weakly present at 1 20 A lumbar puncture revealed 88 red blood cells/mm Urinalysis revealed an occasional red blood cell per high power field The chest roentgenogram revealed calcified lymph nodes in the right hilum and a normal cardiac silhouette The electrocardiogram was normal. Repeat echocardiography (Fig 1) again showed an abnormal aortic valve with variable systolic and/or diastolic leaflet thickening dependent on transducer angulation Leaflet mobility w

From the Dep rtm nts of Med cin and Thoraci Card ascula Surg ry Nati n l Naval Medical C t Bethesd Md

Rec i ed f r public t n F b 28 19 9

Accepted for publicati n Ap 12 1979

Reprint requests Timothy P Blai LCDR MC USNR Box 41 Nat n l Na l Medical Cent r Bethesda Md 20014

*The op nions and asserti ns e p essed are the pri ate ews of th authors nd are n t to be con trued as offi i l or as reflecting the view of the Navy Department

Present address D pt. of C rdiol gy Duk Uni ers ty Med al Cent r Durham N C

N tonal I st tute of All rgy nd Infectiou Diseases N ti al In titutes of H lth, Bethesda Md

Santa Barbara Med cal Fo ndat n Clinic Sa ta Barb r C lif

000? 8 03/80/060 83 + 06$00 60/0 © 1980 The C V Mosby Co

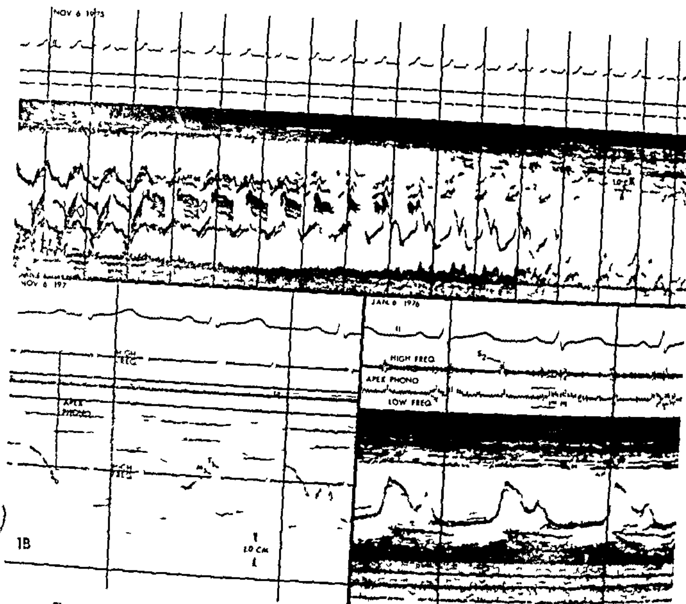


Fig 1 A The initial *portion* of the echocardiographic sweep shows abnormal systolic thickening *(open arr u head)* of the n n coronary *cusp* As the transducer is angled inferiorly abnormal echoes appear first in the midline *(open arr w head)* and then in the left ventricular outflow tract *(closed arrow head)* The left atrial and l ft ventricular dimen ions are *normal B* A simultaneous mitral valve echophonocardiogram at rapid paper speed illu trates the normal QRS *mitral valve* closure interval (approximately u) msec) present on admis ion and that both component of the *first heart* ound (M T₁) are well preserved *C* A simultaneous mitral valve echophonocardiogram recorded *ju t* pri r to aortic valve replacement shows shortening of the QRS mitral valve closure interval (approximately *i0 msec*) and the concomitant appearance of both a presystolic Austin Flint murmur *(brack et)* an l softening *of the* mitral component of the first heart sound Time lines = 1 0 sec

normal The dis t lic echoes w re variabl y ccentric depend ing *on transducer* angulati n On sweeping fr m th *aorta to* mitral valve *the* ab n rmal h es were n t l t *extend into* the l ft *ventricular outfl w* tra t alth ugh n dia tolic high frequency oscillations were n ted *There* wa dis t lic flutter ing of the mitral valve Left entricular l men i ns and calculated ejection fracti n w r *normal* A QRS t mitral valve cl sure int rval wa n rmal *at* n se Multiple cultures of l lood urine and *st m l* t t ris an l fungi were negative

Despite persistently negative l lood cultures, the su pici n of l acterial endocarditis prompted a two week trial of *intra* venous penicillin and gentamicin from November *1? to* ? 197 , and a one week trial of vancomycin from December l to 8 197 , Neither course of antil iotics modified the patient s daily hectic fevers to 38 C On November 7 19 , complement fixation titers to histopla ma yea t and mycelial phase anti gens were 1 64 titers to bla tomyces an l coccidioides ant gen were 1 C1 and 1 8 respectively Repeat titers on November 30 19 simultaneously tested with the serum from November

revealed a rise to 1 256 and 1 512 for histoplasma yeast and mycelia with no change in blastomyces titer Skin tests with intermediate strength tuberculin PPD histoplasmin coccidioidin and streptokinase-streptodornase were all negative A liver biopsy on November 23 1975 revealed noncaseating granulomas containing rare structures consistent with *H capsulatum* culture was unsuccessful because of bacterial overgrowth Granulomas were also present in bone marrow biopsy material. On December 10 1975 intravenous amphotericin B was begun and the fever gradually subsided over eight days On December 15 a bone marrow culture was positive for *H capsulatum*

During December 1975 and early January 1976 the patient remained free of symptoms of congestive heart failure but progressive left ventricular enlargement was noted by chest roentgenography and by echocardiography Left atrial enlargement was noted on echocardiography An apical presystolic Austin Flint murmur developed and the QRS to mitral valve closure interval shortened to a minimum of 30 msec The calculated ejection fraction remained normal.

On January 7 1976 he underwent an uneventful replacement of the aortic valve with insertion of a Hancock porcine prosthetic valve The left atrial pressure at surgery was 24 mm. Hg The resected aortic valve was tricuspid but markedly deformed by vegetations on each cusp with small perforation in the right and left coronary cusps (Fig 2) Flail leaflets were not present Histopathologic examination of the valve revealed organisms consistent with *Histoplasma* (Fig 3) and culture subsequently grew *H capsulatum*

Postoperative recovery was uneventful and a total of 2 gm of intravenous amphotericin B was administered over two months. Antibody determinations in September 1977 revealed a *H capsulatum* yeast titer of 1 16 and a mycelial phase titer of 1 8 At follow up 24 months after valve replacement the patient was asymptomatic had gained 16 kg and was working as a watchman The prosthetic valve functioned normally

Discussion

The present case is an example of disseminated histoplasmosis presenting as blood culture negative aortic valve endocarditis The clinical features of the other reported cases of *H capsulatum* endocarditis are presented in Table I All cases with the exception of one from rural Canada were inhabitants of the eastern United States or the Ohio Mississippi Valley region Splenomegaly was present in 52% anemia in 75% normal leukocyte count in 85% leukopenia in 10% and leukocytosis in 5% Microscopic hematuria was present in 50% and the erythrocyte sedimentation rate was elevated in 92% Blood culture was positive in only one case [21]

A murmur was present in 68% of the cases As in the present case the aortic valve was most frequently the site of infection The aortic valve alone was involved in 10 cases the mitral valve



Fig 2 Aortic valve demonstrating fungal vegetations and multiple leaflet perforation.

alone in five both aortic and mitral valves were involved in two the tricuspid valve was involved in two and the papillary muscle and left ventricle in one Eleven of 22 cases including the present one did not have underlying valvular disease When pre existing heart disease was present it was most frequently rheumatic (six cases) including one case of mitral stenosis associated with an atrial septal defect Luetic aortic valvulitis with an aortic aneurysm [1] bicuspid aortic valve and left atrial myxoma each occurred once One patient s heart was reported as abnormal but the lesion was not described No abnormality was noted in the remaining 12 cases

Cutaneous delayed hypersensitivity reaction to intradermal *H capsulatum* antigen is of no value in the diagnosis of disseminated histoplasmosis Of the ten cases including the present one in which response to *H capsulatum* skin testing was reported only one had a positive response

Complement fixation testing provided the first indication of the etiology in the present case The initial titers were 1 64 to both the yeast and mycelial phases of *H capsulatum* The titer rose to 1 256 following a histoplasmin skin test Although skin testing is known to elevate serologic titers Kaufman and colleagues[27] have shown that a maximum rise to a titer of only 1 32 occurred with skin testing in previously sensitized individuals Although possible it therefore seems unlikely that skin testing resulted in the rising titers demonstrated in the present case The

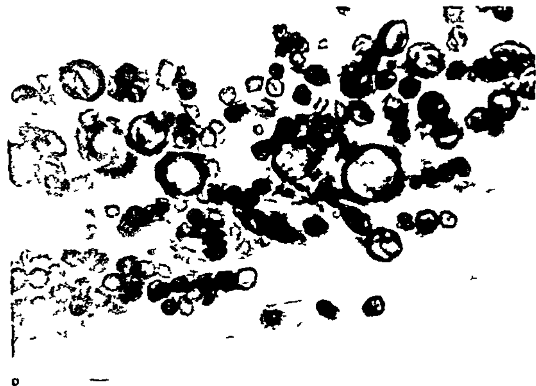


Fig 3 Masses of *H capsulatum* yeast are present in photomicrograph of section of aortic valve (Methenamine silver stain original magnification × 60)

response to therapy is documented by a gradual fall to a *H capsulatum* yeast titer of 1 16 and a mycelial titer of 1 8

Large artery embolization can be an important presenting manifestation of *H capsulatum* endocarditis Two of the surviving patients[15 17] were diagnosed by histologic examination of femoral artery emboli Our patient presumably suffered a cerebral embolus which prompted his second hospitalization but no peripheral emboli were available for examination Antemortem diagnosis has also been established by biopsy of the liver[4] gingiva and epiglottis Although biopsy of the liver in the present case revealed organisms consistent with *H capsulatum* attempts at culture were unsuccessful because of bacterial contamination A positive bone marrow culture ultimately established the diagnosis in the present case as it did in one other successfully treated case[20]

Echocardiography is a useful tool in the detection of fungal endocarditis of the aortic and mitral valves and in the evaluation of hemodynamic severity The abnormal echoes from the aortic valve in the present case are typical of the valvular vegetations described both in fungal and bacterial endocarditis No high frequency diastolic oscillations of the echoes were seen but they did extend into the left ventricular outflow tract (Fig 1) At operation flail leaflets were not seen and these echoes undoubtedly reflected the vegetations that extended below the leaflets into the left ventricular outflow tract

Presystolic closure of the mitral valve in the absence of a prolonged PR interval is a reliable echocardiographic sign of acute aortic regurgitation with a rising left ventricular diastolic pressure In this patient the interval was initially normal but progressively shortened reaching a low of 30 msec prior to surgery This interval change occurred in the setting of an unchanged PR interval (160 msec) and correlated well with the appearance of an apical Austin Flint rumble Although mitral valve closure never preceded the onset of the QRS complex the interval of 30 msec is well below the range of normal reported by Waider and Craige[7] together with the change in heart size this reflected increasingly severe aortic regurgitation The decision to replace the aortic valve in this patient was supported by recent studies emphasizing the importance of early valve replacement when heart failure super

Table I Histoplasma endocarditis

Reference	Case	Date	Age	Sex	Cardiac murmur	Time to diagnosis (months)	Diagnostic methods	Valve involved	Previous cardiac disease	Outcome
1	1	1939	17	M	–	7 0	NA	LV papillary muscle LV anterior surface	None	Death
2	2	1939	53	M	–	NA	Necropsy	Aortic	None	Death
3	3	1938	54	M	+	7.5	Necropsy	Aortic	Syphilitic aortic valvulitis & aortitis	Death
4	4	1942	47	M	+	9	Liver bx	Aortic Mitral	RHD	Death
5 6	5	1944	59	M	–	9	Necropsy	Tricuspid	None	Death
7	6	1945	55	F	+	4	Necropsy	Mitral	MS present	Death
8 9	7	–	32	F	+	13	NA	Aortic	Not described	Death
8 10	8	1949	64	M	–	34	Gingival	Tricuspid	None	Death
8	9	–	39	M	+	8	NA	Aortic	None	Death
11	10	1954	44	M	+	10	Necropsy	Aortic	Bicuspid aortic valve	Death
12	11	1955	56	M	–	31	Necropsy	Aortic	None	Death
12	12	1955	35	M	+	21	Necropsy	Aortic	None	Death
13	13	1956	50	M	+	3	Pharyngeal bx	Mitral	RHD	Death
14	14	1957	37	F	+	6	Necropsy	Aortic	RHD	Death
15	15	1959	27	F	+	10	Femoral embolectomy	Mitral	None	Cured with 4.2 grams of amphotericin B
16	16	1963	50	M	+	9	Necropsy	Mitral	ASD RHD	Death
17	17	1963	61	M	–	NA	Femoral embolectomy	NA	None	Cured with 4 0 grams amphotericin B
18	18	1965	3	M	+	2	Necropsy	Mitral	RHD	Death
19	19	1965	59	M	–	4	Necropsy	Aortic	None	Death
20	20	1968	45	M	+	2	Bx of epiglottis ulcer	Aortic Mitral	None	Cured with 1 49 grams of amphotericin B
21	21	1977	48	F	+	7	Echocardiography Complement fixation serology		Atrial myxoma	Cured with 2 1 gms of amphotericin B & atrial myxoma resection
Present case	22	1975	22	M	+	8	Bone marrow bx	Aortic	None	Cured with 2 0 grams of amphotericin B & aortic valve replacement

Abbreviations NA = not availabl LV = left v ntricle RHD = rh matic heart dise se MS = mitral stenosis bx = bi p v M = male F = f male + = present – = absent

venes during the course of bacterial[3 …] or fungal[3] endocarditis

The optimal dosage of amphotericin B for therapy in disseminated fungal infections has not been precisely defined Two grams of amphotericin B have been curative in disseminated histoplasmosis [1 2] *H capsulatum* endocarditis has been successfully treated medically with 4 2 gm [ ] 4 0 gm [1] 1 49 gm and 2 1 gm of amphotericin B Although our patient showed a favorable clinical response to the administration of 0 72 gm amphotericin B over four weeks valve replacement was necessitated by hemodynamic deterioration and viable *H capsulatum* were demonstrated in the valve removed at surgery This apparent failure of medical therapy could have resulted from poor penetration of amphotericin B into the fungal vegetations[35] despite presumably adequate serum antibiotic levels

H capsulatum endocarditis should be managed similarly to other forms of endocarditis Since cases have been successfully treated medically [15 … 0] valvular replacement is probably only indicated when there is hemodynamic deterioration recurrent embolization or failure of medical therapy alone

Summary

Endocarditis is a rare manifestation of disseminated *Histoplasma capsulatum* infection A 22 year old man presented with a seven month history of fever weight loss and progressive aortic insufficiency The diagnosis of *H capsulatum* was suggested by a diagnostic rise in complement fixation titers and positive echocardiographic findings The diagnosis was confirmed prior to surgery by positive bone marrow culture Progressive congestive heart failure necessitated replacement of the aortic valve which subsequently grew *H capsulatum* In this case a combination of amphotericin B therapy and valve replacement was curative

REFERENCES

Humphrey A A Reticuloendotheliosis cytomycosis (histoplasmosis of Darling) Arch Intern Med **65** 902 1940

Moore M Morphologic variation in tissue of the blastomycoses and histoplasmosis Am J Path **31** 1049 1955

3 Beamer P R Reinhard E H Goodof II Vegetative endocarditis caused by higher bacteria and fungi Am Heart J **29** 99 1945

4 Broders A C Dochat G R Herrell W E and Vaughn J D Histoplasmosis producing vegetative endocarditis review of literature with report of a case J.A.M.A. **122** 489 1943

5 Kemper J W and Bloom H J Histoplasmosis report of a case J Oral Surg **2** 167 1944

6 Parsons R J and Zarafonetis C J D Histoplasmosis in man report of seven cases and a review of seventy one cases Arch Intern Med **75** 1 1945

7 Fawell W M Browns H C and Ernstene A C Vegetative endocarditis due to *Histoplasma capsulatum* Cleveland Clin Q 18 305 1951

8 Binford C H Histoplasmosis tissue reactions and morphologic variation of the fungus Am J Clin Path **25** 2 1955

9 Zimmerman L E Some contributions of the histopathological method to the study of fungus disease Trans N Y Acad Sci **19** 338 195

10 Sulak M H Clinicopathologic conference U S Armed Forces Med J **8** 70 1957

11 Berman B Histoplasmosis endocarditis, Sinai Hosp J **9** 4 1960

12 Merchant R K Louria D B Geisler P H Edgcomb J H and Utz J P Fungal endocarditis review of the literature and report of three cases Ann Intern Med **48** 21 1958

13 Palmer R L Geraci J E and Thomas B J *Histoplasma* endocarditis Arch Intern Med **110** 3 9 1962

14 Haust M D Wlodek G K and Parker J O *Histoplasma* endocarditis Am J Med **32** 160 196

15 Derby B M Coolidge K and Rogers D E *Histoplasma capsulatum* endocarditis with major arterial embolism Arch Intern Med **110** 101 1

16 Korn M F C in tl nce of n t *Histoplasma capsulatum* vegetative endocarditis of the mitral valve and the Lutembacher syndrome Circulation **32** 5? 1965

17 Segal C Wheeler C G and Tompsett R *Histoplasma* endocarditis cured with amphotericin N Engl J Med **280** 206 1969

18 Hartley R A Remsberg J R S and Sinaly N P *Histoplasma* endocarditis case report and review of the literature Arch Intern Med **119** 527 1967

19 Gerber H J Schoonmaker F W and Vazquez M D Chronic meningitis associated with *Histoplasma* endocarditis N Engl J Med **275** 74 1966

20 Drutz D J Spickard A Rogers D E and Koenig M L Treatment of disseminated mycotic infections a new approach to amphotericin B therapy Am J Med **45** 405 1968

21 Rogers E W Weyman A E Noble R J and Brum S C Left atrial myxoma infected with *Histoplasma capsulatum* Am J Med **64** 683 1978

22 Kaufman L Terry R T Schubert J H and McLauchlin D Effect of a single histoplasmin skin test on the serological diagnosis of histoplasmosis J Bacteriol **94** 798 1967

23 Furcolow M C Tests of immunity in histoplasmosis N Engl J Med **268** 357 1963

24 Gottlieb S Khuddus S A Balooki H Dominguez A E and Myerburg R J Echocardiographic diagnosis of aortic valve vegetations in *Candida* endocarditis, Circulation **50** 826 1974

25 Arvan S Cogin N Levitt B and Kleid J J Echocardiographic findings in a patient with *Candida* endocarditis of the aortic valve Chest **70** 300 1976

26 Gomes J A C Calderon J Lajam F Sakurai H Freidman H S and Tatz J S Echocardiographic detection of fungal vegetations in *Candida parasilopsis* endocarditis Am J Med **61** 273 19 6

27 Pasternak R C Cannon D S and Cohen L S Echocardiographic diagnosis of large fungal verrucae attached to mitral valve Br Heart J **38** 1209 19 6

28 Dillon J C Feigenbaum H Konecke L L Davis R H and Chang S Echocardiographic manifestations of valvular vegetations Am Heart J **86** 698 19 3

29 Mann T McLaurin L Grossman W and Craige E Assessing the hemodynamic severity of acute aortic regurgitation due to infective endocarditis N Engl J Med **293** 108 1975

30 Waider W and Craige E First heart sound and ejection sounds echocardiographic and phonocardiographic correlation with valvular events Am J Cardiol **35** 346 1975

31 Griffin F M Jones G and Cobbs C V Aortic insufficiency in bacterial endocarditis Ann Intern Med **76** 23 1972

32 Parrott J C W Hill J D Keith W J and Gulode F The surgical management of bacterial endocarditis a review Ann Surg **183** 289 19 6

33 Utley J Mills J and Roe B B The role of valve replacement in the treatment of fungal endocarditis J Thoracic Cardiovasc Surg 69 ?? 19 5

34 Parker J D Sarosi G A Doto L L Bailey R E and Tosh F G Treatment of chronic pulmonary histoplasmosis a National Communicable Disease Center cooperative mycoses study N Engl J Med *283* 2 19 0

35 Rubenstein E Noriega E R Simberkoff M S and Rahal J J Tissue penetration of amphotericin B in *Candida* endocarditis, Chest **66** 3 19 4

Clinical pathologic conference

Primary pulmonary hypertension

Stephen M Factor M D
Joseph Reichel M D
Bronx N Y

CLINICAL SUMMARY This 60 year old hypertensive non diabetic woman had a 3 year history of dyspnea on exertion orthopnea and pedal edema treated with digitalis and diuretics She was first hospitalized in May 1976 for surgical correction of an incarcerated abdominal hernia At that time she was noted to have a prominent mitral regurgitation murmur with cardiomegaly and compensated congestive heart failure There was no history of acute rheumatic fever or myocardial infarction

The patient was lost to follow up for several months during which time she ceased taking her diuretic She developed progressive pedal edema dyspnea on exertion and paroxysmal nocturnal dyspnea She had occasional episodes of precordial pressing chest pain radiating to the arms associated with nausea and diaphoresis and never lasting more than 5 to 15 minutes The pain was not pleuritic or positional and was relieved by nitroglycerin When her symptoms worsened she sought medical attention and she was admitted to the hospital

On physical examination the patient was obese dyspneic and cyanotic in obvious respiratory distress The pulse was regular and 108/minute respirations were 40/minute and the blood pressure was 140 mm Hg systolic by palpation She was afebrile There was jugular venous distension at 30 degrees There were mild hypertensive changes in the fundi The chest was dull to percussion one third of the way up on the right and one fourth of the way up on the left On auscultation there were decreased breath sounds at both bases with a bronchovesicular quality and no rales or ronchi The point of maximal cardiac impulse was in the fifth intercostal space in the anterior axillary line There was a Grade V/VI holosystolic apical murmur with a thrill radiating to the axilla No diastolic murmur or gallops were heard S and S sounds were diminished The abdomen had a fluid wave shifting dullness and bulging flanks The liver edge was palpated four finger breadths below the right costal margin The extremities revealed 3+ pitting edema to the knees and cyanosis The remainder of the physical examination was unremarkable

The patient had a hematocrit of 54 3 volumes per cent and a hemoglobin of 18 gm /100 ml The white blood count was normal The electrolytes were sodium 147 mEq /L potassium 4 7 mEq /L chloride 109 mEq /L and CO_2 14 mEq /L The blood glucose was 238 mg per cent the blood urea nitrogen 23 mg per cent and the creatinine 1.2 mg per cent Total bilirubin was 2 1 mg per cent and direct bilirubin was 1 0 mg per cent The prothrombin time was slightly elevated The serum glutamic oxaloacetic transaminase was 54 units the lactic dehydrogenase was 361 units and the creatine phosphokinase was normal Urinalysis showed 3+ protein Arterial blood gases on room air revealed a pH of 7 31 an oxygen partial pressure (PO_2) of 24 5 mm Hg and an oxygen saturation of 67% The electrocardiogram showed normal sinus rhythm PR interval 0 12 QRS interval 0 09 axis + 150 degrees P mitrale and bigeminy The chest x ray revealed bilateral pleural effusions and cardiomegaly An echocardiogram showed right ventricular hypertrophy

From the Departments of Pathology and Medicine Albert Einstein College of Medicine and The Bronx Municipal Hospital Center Bronx, N Y

Received for publication June 18 1979

Reprint requests Stephen M Factor M D Dept. of Pathology Albert Einstein College of Medicine 1300 Morris Park Ave Bronx N Y 10461

0002-8703/80/060789 + 10$01 00/0 © 1980 The C V Mosby C

concentric left ventricular hypertrophy with a good ejection fraction and normal left atrial size

The patient was intubated and treated with 70% oxygen The arterial blood gases improved and the patient looked and felt better However she required a constant dopamine drip infusion to maintain blood pressure at 100 mm Hg Attempts to insert a Swan Ganz catheter were unsuccessful and resulted in trauma to the left brachial artery with subsequent thrombosis of the radial artery The vessel was repaired under local anesthesia with resection of a small portion of brachial artery removal of thrombus and end to end anastomosis Good blood flow was established in the extremity She was given 5 000 units of heparin She developed upper gastrointestinal bleeding and bleeding from the endotracheal tube but this stabilized spontaneously

Approximately 20 hours after admission the patient had a respiratory arrest and an anoxic seizure Attempts at resuscitation were initially successful however she died several hours later

Clinical discussion

DR JOSEPH REICHEL This case defies concise analysis The data which must be reconciled are the mitral regurgitation murmur unexplained prior shock cardiomegaly and P mitrale without left atrial enlargement polycythemia hypoxemia right ventricular hypertrophy and the absence of pulmonary congestion

I will take the position that this patient had right ventricular hypertrophy and pulmonary hypertension The data which substantiate this are as follows In May 1976 there was a wandering atrial pacemaker at a rate of 68 and an S_1 Q3 T3 pattern with ST T wave depression in Leads II III aV_F and V to V In March 1977 the electrical axis was +150 degrees with R greater than S in Leads V and V_2 There was a strain pattern with an incomplete right bundle branch block The echocardiogram showed right ventricular hypertrophy concentric hypertrophy of the left ventricle with a good ejection fraction and normal left atrial size

In approaching the causes of pulmonary hypertension it is necessary to start at the aortic valve and work back to the lung and the pulmonary vasculature We will have to consider rheumatic and calcific aortic stenosis as well as idiopathic hypertrophic subaortic stenosis We shall have to include in our discussion dilatation of the mitral ring due to left ventricular failure and hypertension Occult mitral stenosis and diseases which mimic occult mitral stenosis such as atrial myxoma and atrial thrombus will enter our differential The question of the patient s mitral regurgitation whether due to cardiomyopathy rheumatic fever papillary muscle rupture or dysfunction or rupture of chordae tendineae will have to be examined Transmission of high pressure to the right ventricle through a ventricular septal defect possibly due to myocardial infarction and an aneurysm of the sinus of Valsalva will have to be mentioned It is unlikely that this clinical picture is produced by an atrial septal defect. Pulmonary venoocclusive disease primary pulmonary hypertension and recurrent pulmonary emboli also have to be considered At this point I wish to mention primary pulmonary diseases as a cause of polycythemia and right ventricular hypertrophy only to dismiss this group of conditions There is no history of cough, sputum production tuberculosis occupational exposure or other prior pulmonary disease In addition we will mention only to exclude the remote possibility that this patient who died with abdominal distention and a guaiac positive nasogastric aspirate had mesenteric vascular disease or rupture of an aortic aneurysm

Aortic stenosis is an unlikely diagnosis because of the brisk carotid pulses the absence of a diamond shaped cardiac murmur and the presence of right ventricular hypertrophy Although the murmur of aortic stenosis in an elderly person may occasionally radiate to the apex axillary radiation with a thrill is extremely unlikely Idiopathic hypertrophic subaortic stenosis can probably be ruled out because of the negative echocardiogram in 1977 the absence of severe asymmetrical left ventricular hypertrophy and the lack of a Q wave in Leads II III aV_F and the left precordium Furthermore this fails to explain the presence of right axis deviation and right ventricular hypertrophy Cardiomyopathy may mimic or cause severe mitral regurgitation however, with no history of recurrent arrhythmias and with the presence of severe right axis deviation this diagnosis is low on our differential list

We must give more thought to the possibility of silent mitral stenosis with extreme pulmonary vascular obstruction This condition is characterized by dyspnea orthopnea and syncope right ventricular failure may be present Of importance the pulmonary artery is usually dilated and there is pruning of peripheral vessels which was not observed in our case Although there may be no history of rheumatic fever a right ventricular heave an opening snap of the mitral valve an increase in intensity of the first sound and the pulmonary component of the second heart sound and an increase in size of the left atrium pulmonary artery and right ventricle are commonly seen P mitrale may or may not be observed and atrial fibrillation is almost invariably present Because of the regular rhythm and normal sized left atrium I tend to exclude silent mitral stenosis

A more likely diagnosis especially because this is a CPC is a cardiac tumor specifically an atrial myxoma[3,5] Atrial myxomas comprise 30 to 50% of cardiac tumors They are more common in women than men in a 3 to 1 ratio and 75% are in the left atrium Valvular obstruction may simulate mitral or tricuspid stenosis The murmur of mitral regurgitation or tricuspid regurgitation also has been described Right atrial myxomas may cause or simulate pulmonary hypertension and may cause increased hematocrit Clubbing and cyanosis with a variable right to left shunt associated with a change in position may occur if there is a patent foramen ovale or an atrial septal defect Systemic effects including fever leukocytosis weight loss elevation of the sedimentation rate and hyperglobulinemia are commonly seen in atrial myxoma and were not present in our patient The absence of abnormal findings in the left atrial echocardiogram also mitigate against atrial myxoma however we cannot rule out a right atrial myxoma projecting into the left atrium through an atrial septal defect or multiple atrial myxomata In a review of left atrial myxoma 28 of 40 patients had pulmonary hypertension 22 of 40 had a systolic murmur and 10 had pulmonary embolism

One entity which has a clinical appearance similar to atrial myxoma is atrial thrombus Here sudden death may occur usually in the presence of mitral stenosis and atrial fibrillation There is usually severe pulmonary congestion and past or recent peripheral emboli The symptoms are eased by leaning forward and there may be changing murmurs and periodic numbness of the hand and feet Patients may have an accelerated downhill course The negative echocardiogram and the absence of atrial fibrillation changing murmurs and episodes of numbness are against this diagnosis

Calcification of the mitral ring may elevate the valve leaflets stretch the chordae tendineae and produce mitral regurgitation The picture of progressive pulmonary congestion and right ventricular failure over 4 to 8 years may be seen however in the absence of calcification on x ray we cannot make this diagnosis in our patient

In distinguishing severe from mild mitral regurgitation the following factors must be considered In severe mitral regurgitation there is a palpable left ventricular heave a loud S sound evidence of left atrial abnormality a wide split S sound and usually a history of rheumatic fever In contrast in mild mitral regurgitation there is no increase of left ventricular activity no sounds are heard in diastole there is normal left atrial size and no symptoms of congestive heart failure or history of rheumatic fever are present

We should give some consideration to the question of mitral regurgitation due to coronary artery disease Rupture of a papillary muscle or chordae tendineae attachment occurs in 1% of myocardial infarctions whereas papillary muscle dysfunction occurs in 25% Rupture of the body of a papillary muscle causes rapid pulmonary edema shock and death In contrast rupture of a single head of a papillary muscle produces a sudden catastrophe in a patient recovering uneventfully from myocardial infarction There may be a Grade 3 or 4 murmur radiating to the axilla with a thrill an S and S gallop and a small left atrium Usually the electrocardiogram shows a myocardial infarction The pulmonary artery pressure and pulmonary vascular resistance are high and the prognosis is very poor Fewer than 20% of patients survive two weeks Without surgery there is usually death from congestive heart failure within a short time

Let us consider papillary muscle dysfunction[8] This entity may occur as a result of distortion of the normal spatial relations between the papillary muscle the valve leaflets and the ventricle Dilatation of the ventricle idiopathic hyper



Fig 3 The opened right heart reveals marked ventricular [illegible]phy with prominence of the papillary muscle and [illegible] The ventricular wall measures up to 1 cm [illegible] The tricuspid valve ring the atrium and the [illegible] are dilated Focal fibroelastosis of the endocardium [illegible] patches on the ventricular surface The [illegible] valve leaflets are minimally thickened and the septal [illegible] has an irregular perforation *(arrow)* which probably [illegible] healed infective endocarditis The roughened atrial endocardium [illegible] this lesion indicative of valvular insufficiency cannot be appreciated from this view

trophic subaortic stenosis the click murmur syndrome [illegible] fibroelastosis and carcinoid tumor may cause this dilatation There may be intrinsic abnormalities of the papillary muscles due to coronary atherosclerosis abscess or vasculitis In addition there may be functional abnormalities of the papillary muscle Asynchrony between contraction of the papillary muscle and left ventricular contraction may cause papillary muscle dysfunction The symptoms are generally those of coronary artery disease There may be chest pain and pulmonary edema with varying degrees of mitral regurgitation There is usually a soft high pitched musical holosystolic Grade I II murmur and there may be a click late systolic murmur syndrome There is often evidence of myocardial infarction and S T depression in the lateral precordial leads Ventricular function is frequently bad Because our patient had a rather loud murmur with a thrill and because of the absence of electrocardiographic evidence of myocardial infarction it is unlikely that our patient's problems were caused by papillary muscle dysfunction

Mitral regurgitation due to rupture of the chordae tendineae may be due to [illegible] bacterial endocarditis [illegible] heart [illegible] rheumatic congenital coronary [illegible] or isolated [illegible] rupture In rheumatic heart disease sudden worsening may occur and the syndrome may be associated with atrial fibrillation or dilatation of the left atrium There is often significant aortic and mitral regurgitation Isolated rupture of the chordae tendineae commonly occurs in males aged 40 to 60 There is no history of rheumatic fever and there may be sudden dyspnea and pulmonary edema There is a sudden loud harsh systolic murmur The left atrium is normal [illegible] and there is no cardiomegaly Rhythm is sinus despite the presence of severe mitral regurgitation and there is usually a prominent S and S sound with a brief diastolic murmur The second pulmonary sound is widely split and there may be minimal symptoms including episodic dyspnea and chest pain The echocardiogram usually shows preservation of ventricular contractility Because the murmur of spontaneous rupture of the chordae tendineae usually radiates from the apex to the aortic area and because we cannot explain right ventricular hypertrophy on this basis I rule out this diagnosis In one review of 23 patients with rupture of a head of the papillary muscle or of chordae tendineae 22 of 23 patients had sinus rhythm and a harsh systolic murmur In five cases there was radiation to the axilla In all cases the chest x ray showed pulmonary edema which further rules against this diagnosis in our case

We must also consider rupture of the ventricular septum which can occur a few hours to six weeks after myocardial infarction producing dyspnea and shock [1] There is biventricular failure and a loud holosystolic murmur in the third fourth and fifth interspace at the left sternal border In one third of cases the murmur radiates to the apex The left to right shunt may produce pulmonary hypertension however most individuals have evidence of myocardial infarction and less than 15% of patients survive two months

Even less likely would be an aneurysm of the sinus of Valsalva which usually produces a continuous murmur over the left precordium in the third to the fourth interspace Right axis deviation is usually not seen

Much more consideration should be given to the possibility of primary pulmonary hypertension [11] In one review of 23 patients the disease was more common in females in a ratio of five to one The age of the patients ranged between 11 and 56 years Syncope which has been stressed in



Fig 2 This section of main pulmonary artery reveals striking intimal thickening *(the region above the arrows)* with changes typical of atherosclerosis including fibrosis and lipid deposition (the intimal clefts represent dissolved cholesterol) The underlying media *(stained black)* has compressed elastic lamellae and is focally thinned This degree of pulmonary atherosclerosis is rare except in cases of severe pulmonary hypertension (Verhoeff van Gieson elastic tissue stain original magnification × 8)

this entity was only seen in six patients Seven patients had Raynaud s disease and three patients had arthritis A systolic murmur which may be due to tricuspid regurgitation was seen in 10 patients and 12 patients had thromboemboli The etiology of this entity is not known Suggested causes include congenital lesions collagen vascular diseases multiple small emboli vasospasm or familial tendency Wagenvoort and Wagenvoort examined material from 156 patients in whom the diagnosis of primary pulmonary hypertension had been made In 31 patients there was evidence of organizing thrombi intimal fibrosis and intra arterial septa—suggesting thromboembolic disease A small number of patients had veno occlusive disease sarcoidosis chronic obstructive pulmonary disease and schistosomiasis In 110 cases there was medial hypertrophy intimal fibrosis arteritis and morphologic changes of pulmonary hypertension identical to those seen in individuals with congenital heart disease The major argument against primary pulmonary hypertension in this case is the patient s age Most patients with this entity are younger

We must briefly consider pulmonary veno occlusive disease in which there is severe venous intimal fibrosis and capillary dilatation ' Arterial changes may be similar to those seen in primary pulmonary hypertension and in fact this disease is considered by some to be a variant of this condition In all instances however the x ray shows pulmonary edema which our patient did not have

I think it most likely that our patient had recurrent multiple pulmonary emboli ' The electrocardiogram in acute pulmonary embolism shows an $S_1Q_3T_3$ pattern in 12% of patients a right bundle branch block in 9% of patients and right axis deviation in 7% of patients[21] These changes are due to pulmonary hypertension and return to normal when pulmonary pressures drop

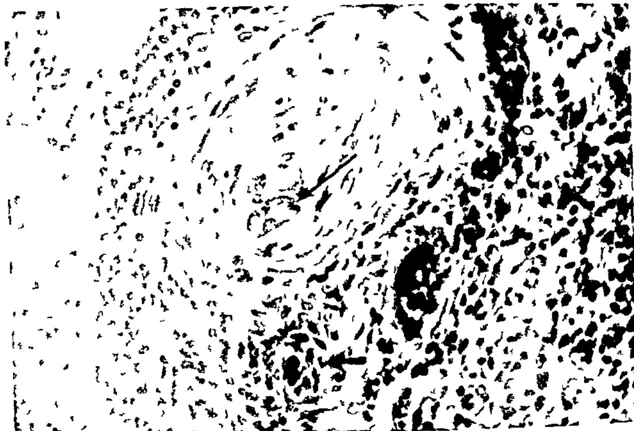


Fig 3 This small muscular pulmonary artery is almost completely occluded by concentric intimal fibrosis. The small [illegible] lumen is filled with a recent fibrin thrombus *(thin arrow)*. Surrounding the vessel and presumably attached to it is a portion of a plexiform lesion *(thick arrow)* (Hematoxylin and eosin original magnification × [illegible])

The LDH and bilirubin are often elevated as demonstrated by our patient. Chest x ray abnormalities in acute pulmonary embolism are very common but non specific. One may see consolidation, pleural effusions, prominence of the pulmonary artery segments, atelectasis and focal oligemia. Hypoxemia in pulmonary embolism is commonly seen and is thought to be due to a shift of distribution of perfusion to areas of low ventilation perfusion ratio. In one study of 12 individuals from 8000 consecutive autopsies where congestive heart failure was found without any other cause, all patients had dyspnea, one patient had syncope, 10 of the patients were cyanotic, five had tricuspid murmurs, all of the patients had normal sinus rhythm and 11 patients had right ventricular hypertrophy. All of the patients showed organized emboli in the tertiary arteries of both lungs which were often indistinguishable from in situ thrombosis. Half of the patients had thrombi in the veins of the legs and a small percentage had intracardiac thrombi.

It is therefore my impression that our patie[nt] had recurrent multiple pulmonary emboli[s]m wi[th] chronic cor pulmonale. There may be tricusp[id] regurgitation due to pulmonary hypertensi[on] mimicking mitral insufficiency, or there may [in] fact be mitral regurgitation due either to sil[ent] rheumatic heart disease, ruptured chordae ten[di]neae or hemodynamic causes. Finally [illegible] ventricular hypertrophy secondary to hypert[en]sive cardiovascular disease, chronic passive co[n]gestion of the viscera and gastrointestinal hem[or]rhage due to stress ulcers will probably [be] found.

Autopsy findings

Dr Stephen M Factor: Dr Reichel's inc[isive] and superb discussion of this difficult c[ase] mirrors many of the diagnoses which we [illegible] pathologists must consider when dealing w[ith] pulmonary hypertension and cor pulmonale [illegible] particular we must differentiate three conditi[ons] which may have identical clinical features [illegible] have distinct histopathological changes.

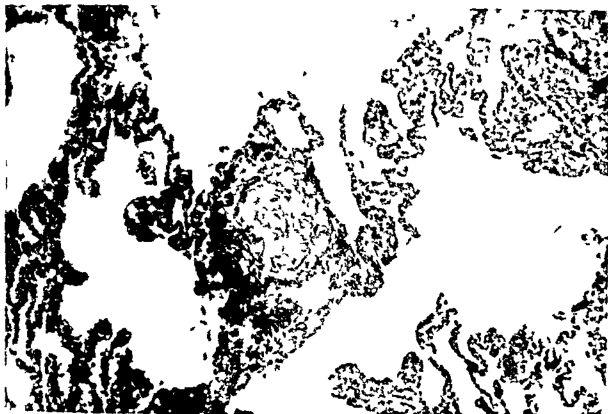


Fig 4 This low power view of the lung shows a muscular pulmonary artery with a narrowed lumen secondary to medial hypertrophy and intimal fibrosis. The pulmonary parenchyma with the exception of mild focal septal thickening is unremarkable (Hematoxylin and eosin original magnification ×78)

chronic recurrent pulmonary thromboembolism (2) pulmonary veno occlusive disease and (3) plexogenic pulmonary arteriopathy It has been stated[3] that these diseases may only be distinguished by lung biopsy or necropsy Having the advantage of the latter I hope to demonstrate that we can make a specific diagnosis in this case

The postmortem examination revealed evidence of marked right sided heart failure with bilateral pleural effusions ascites and visceral congestion The heart weighed 450 gm and had striking right atrial and right ventricular hypertrophy and dilatation (Fig 1) Focal endocardial fibroelastotic plaques were noted in the right ventricle probably secondary to turbulent flow or mural thrombosis The tricuspid valve ring was dilated most likely accounting for the insufficiency murmur However we also noted a small perforation in the septal leaflet of the tricuspid valve with a jet lesion on the atrial wall above it This perforation was possibly caused by silent endocarditis which subsequently healed Its contribution to the tricuspid insufficiency could not be determined

The three other valves were morphologically normal and there was no evidence of associated stenosis or insufficiency The left ventricular cavity was small due to concentric myocardial hypertrophy secondary to hypertension There was a subaortic muscular bulge with some endocardial thickening however there was inadequate evidence of a friction lesion due to systolic anterior motion of the mitral valve Additionally though we found rare disorganized muscle fibers in the ventricular septum (whorls) they were few enough in number for us to rule out idiopathic hypertrophic subaortic stenosis as the etiology of these changes

The pulmonary artery had severe intimal fibrosis as well as obvious atherosclerotic plaques consistent with pulmonary hypertension (Fig 2) These alterations could be seen grossly in many of the distal branches which were dilated and tortuous out to the pleural surface With the exception of the pulmonary vessels the lungs



Fig 5 A plexiform lesion arising from a medium sized pulmonary artery Note its thin wall and lumen composed of several small vascular channels (arrows) devoid of elastic tissue (Verhoeff van Gieson elastic tissue stain original magnification ×200)

were not remarkable on gross examination and their weight was only slightly increased above the normal range

Histologically three lesions were observed in large numbers of small and medium sized muscular arteries Concentric intimal fibrosis (Fig 3) of varying degrees was present as was isolated medial hypertrophy (Fig 4) If these two alterations were all that we found we would have difficulty in making a definitive diagnosis because these changes may be seen in all forms of pulmonary hypertension However the presence of angiomatoid or plexiform lesions which we saw frequently provided support for our diagnosis These lesions (Figs 5 and 6) which represent localized expansions or aneurysmal dilatations of the muscular pulmonary arteries with pronounced endothelial proliferation in a plexiform pattern are characteristically found in primary pulmonary hypertension Although they may also be seen in long standing left to right cardiac shunt or in rare cases of hepatic cirrhosis in the absence of these conditions they are virtually diagnostic of the disease now known as primary plexogenic arteriopathy[2]

For the sake of completeness the only diagnostic feature that we did not observe in this case which has been reported in plexogenic pulmonary arteriopathy was necrotizing arteritis We did note rare fibrin deposits in vessel walls however true necrosis was absent We also saw occasional organized and recent thromboemboli but these were most often associated with the plexogenic lesions

The presence of thromboemboli raises the question whether all of the lesions that we observed could be secondary to recurrent embolization This is not an unimportant consideration since recurrent emboli can lead to severe pulmonary hypertension In the past some pathologists thought that this was the cause of plexogenic pulmonary arteriopathy However the histopathological changes are different from those in today's case In most cases of recurrent throm

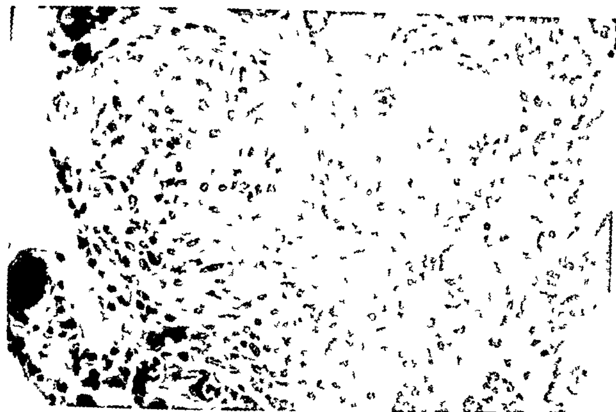


Fig 6 This high magnification of a plexiform or ang m t th t it made up f multiple small vascular channels some of which contain compacted red bl Th re are many proliferated endothelial cells in the lesion which are not associated wi h n H m t xylin and o in original magnification ×5 0)

boemboli leading to pulmonary hypertension the lesions are also found in the muscular branches of the pulmonary arterial tree However character istically the emboli produce eccentric intimal fibrosis fibrous septa and recanalized thrombi occluding the vessels Plexogenic lesions and necrotizing arteritis do not occur Thus the occa sional thromboembolus in our case most likely represents a secondary event occurring in a termi nally ill patient

Regarding the third condition which may produce primary pulmonary hypertension—veno occlusive disease—both the clinical features and the histology in this case allow us to rule out this diagnosis This rare disease generally affects chil dren and young adults It primarily involves pulmonary veins and venules with intimal fibrous tissue proliferation producing vascular obliteration [2] As a consequence of venous obstruction there is distention and tortuousity of capillaries with intraparenchymal hemorrhage and hemosiderin deposition As a secondary event there may be arterial fibrosis and medial hypertrophy but arteritis and plexiform lesions are absent

Therefore we are confident that today s case represents an example of plexogenic pulmonary arteriopathy The marked pulmonary hyperten sion led to the development of massive right ventricular hypertrophy and cor pulmonale The dilatation of the tricuspid valve ring accounted for the insufficiency murmur although there may have been a contribution from the perforation of the tricuspid valve leaflet The cause of death was ultimately a result of right sided congestive heart failure

One final word about the etiology of plexogenic pulmonary arteriopathy Despite extensive spec ulation the etiology remains unknown Most recent studies suggest a primary role for increased pulmonary vasoconstriction or spasm An association of plexogenic pulmonary arteriopathy with Raynaud s phenomenon supports this specu lation In the present case we carefully examined

many systemic vessels in the hope that we might find medial hypertrophy suggestive of spasm However no significant abnormalities were noted Therefore as in most such cases we are left without a specific cause for the unusual alterations in the pulmonary vasculature

REFERENCES

1 Blaunt S G Jr and Vogel J H K Pulmonary hypertension Mod Concepts Cardiovasc Dis 36 61 1967

2 Surawicz B and Nierenberg M A Association of silent mitral stenosis with massive thrombi in the left atrium N Engl J Med 263 423 1960

3 Greenwood W F Profile of atrial myxoma Am J Cardiol 21 367 1968

4 Peters M N Hall R J Cooley D A Lechman R D., and Garcia E The clinical syndrome of atrial myxoma J A M A 230 695 1974

5 Talley K C Baldwin B J Symbas P N., and Nutter D O Right atrial myxoma Am J Med 48 256 1970

6 Goodwin J F Diagnosis of left atrial myxoma Lancet 1 464 1963

7 Castleman B and Kibbee B U Case Records of the Massachusetts General Hospital N Engl J Med 269 969 1963

8 Debusk R F and Harrison D C The clinical spectrum of papillar muscle disease N Engl J Med 281 1458 1969

9 Selzer A Kelly J J Vannitamby M Walker P., Gerbode F and Kerth W J The syndrome of mitral insufficiency due to isolated rupture of the chordae tendineae Am J Med 43 822 1967

10 Raftery E B Oakley C M and Goodwin J F Acute subvalvular mitral incompetence Lancet 2 360 1966

11 Sanders R J Kearn W H and Blaunt S G Jr Perforation of the interventricular septum complicating myocardial infarction AM HEART J 51 736 1956

12 Myer J and Wuukasch D C Aneurysm and fistula of the sinus of Valsalva Ann Thorac. Surg 19 1 0 19 5

13 Blaunt S G Jr Primary pulmonary hypertension, Mod Concepts Cardiovasc Dis 36 67 196

14 Wolcott G Burchell H B and Brown A L, Jr Primary pulmonary hypertension Am J Med. 49 0, 1970

15 Schilder D P., and Harvey W P Confusion of tricuspid incompetence with mitral insufficiency—A pitfall in the selection of patients for mitral surgery AM HEART J 54 352 1957

16 Wagenvoort, C A., and Wagenvoort N Primary pulmonary hypertension A pathologic study of the lung vessels in 156 clinically diagnosed cases Circulation 42 1163 1970

17 Brewer D B., and Humphreys, D R Primary pulmonary hypertension with obstructive venous lesions, Br Heart J 22 445 1960

18 Dexter L. Thromboemboli as a cause of cor pulmonale Bull N Y Acad Med. 41 981 1965

19 Goodwin J F., Harrison C U., and Wilcken D E. L. Obliterative pulmonary hypertension and thromboembolism Br Med J 1 701 1963

20 Owen W R Thomas, W A., Castleman B and Bland, E F Unrecognized emboli to the lungs with subsequent cor pulmonale N Engl. J Med 249 919 1953

21 Stein P D Dalin J E., McIntyre K M Sasahara A A., Wenger N K., and Willis, P W III Electrocardiogram in acute pulmonary embolism Progr Cardiovasc. Dis 17 247 1975

22 Primary pulmonary hypertension Report on a WHO meeting Hatano S and Strasser T., editors, Geneva, 1975 World Health Organization pp 9-37

23 Edwards W D and Edward J E Recent advances in the pathology of the pulmonary vasculature *in* Thurlbeck W M and Abell M R editors The lung Structure function and disease Baltimore 19 8 The Williams & Wilkins Company p 235

24 Naeye R L. Pulmonary hypertension and vascular disease *in* Edwards J E Lev M and Abell M. R., editors The heart Baltimore 1974 The Williams & Wilkins Company p 297

A unified classification for tricuspid atresia*

P Syamasundar Rao M B B S D C H F A C C F A C C
Augusta Ga

Recent de cription of physiologic correction of tricuspid atresia by innovative surgical tech niques by Fontan and Baudet[1] and by Kreu zer and colleagues prompted reexamination of the lesion A symposium on tricuspid atresia held during the 46th Annual Meeting of the Americ n Academy of Pediatrics Scientific Sessions of Sec tion on Cardiology in November 1977 was the result of one such attempt After discussion of the surgical aspects of this complex anomaly the need for a more suitable classification became apparent Tricuspid atresia has been classified on the basis of tricuspid valve morphology roent genographic appearance of pulmonary va cular markings and associated cardiac defects None of the existing classifications is entirely satisfac tory The purpose of this paper is to review the previously proposed classifications and to utilize selected features in a new comprehensive yet unifed approach that offers greater clinical utili ty

I Classification based on morphology of the atretic tricuspid valve

Tricuspid atresia is characterized by congenital agenesis or absence of the morphologic tricuspid valve By far the most common anatomic pattern is the muscular variety a dimple or a localized fibrous thickening may be seen in the floor of the right atrium at the usual site of the tricuspid valve No valvar material can be identified either by gross or microscopic examination Occasional ca e have been reported in which minute valvu lu cu ps may be present but are completely fu ed this has been called the valvular type The atrioventricular portion of the membranous sep um forms the floor of the right atrium at the expected location of the tricuspid valve in the membranous type of tricuspid atresia This anom aly has been described with and without juxtaposition of the atrial appendages In the Ebstein s type three tricuspid valve leaflets are plastered onto the right ventricular wall The leaflets are fused there is no valve orifice The resultant shelf of tissue separates the atrial ized right ventricle from the right ventricular outflow tract The final form occurs with com mon atrioventricular canal in which a leaflet of the common atrioventricular valve completely seals off the only entrance into the right ventri cle

The first formal classification of tricuspid atre sia based on the morphology of the tricuspid valve was proposed by Van Praagh and associates in 1971 (a) muscular type (b) fibrous (membra nous) type and (c) Ebstein s type This classifica tion was later modified by him and by Wein berg as shown in Table I The muscular type constituted 84% of Van Praagh and associates and 76% of Weinberg s cases The membranous type was observed in 8% (three out of 38) of Van Praagh and associates cases and in 12% (four out of 33) of Weinberg s cases but in only 1 5% (one out of 83) of Anderson and colleagues cases The valvular type comprised 5% (four of 83) and 6% (two out of 33) respectively in the cases of Anderson and co workers and in Weinberg s cases The Ebstein s type was found in 8% (three out of 38) of Van Praagh and associates cases and 6% (two out of 33) of Weinberg s cases differing from the frequency rates in our series (one out of 38 2 5%) and in Anderson s series

From the Dep rtment of Pediatrics Sect f Pedi tri C rd logy Med al Coll g f Georgi Augu ta G

Recei ed for publicati O t 10 19 9

Reprint equest P S m nd R M B Pr fesso f Ped trics Sect n of Pedi tri C rd log Medi l C ll g of Geo gi A gu t G 3091

*Presented in part t th 46th An u l Meeting of th Am ri n Acad my of Pediatrics Se ti n on C d ol gy No 5 10 19 New Y k C ty N Y

000? 8703/80/060799 + 06$00 60/0 © 1980 The C V M

Table I Classification of tricuspid atresia based on the morphology of the tricuspid valve*

1 Muscular type
2 Membranous type
3 Valvular type
4 Ebstein type
5 Atrioventricular canal type

*Modified from Van Praagh et al, Van Praagh and Weinberg

Table II Classification of tricuspid atresia based on x-ray appearance of pulmonary vascular markings*

A Decreased pulmonary vascular markings
B Normal or increased pulmonary vascular markings
 Initially normal or increased, latter changing to decreased pulmonary vascular markings

*Adapted from Astley et al and from Dick et al

(two out of 83, 2.5%). Only a few cases of this type have been recorded in the literature, attesting to the rarity of this lesion. The atrioventricular canal type was mentioned briefly by Van Praagh. This type was not found in the original series reported by him nor in the pathologic studies reported by Anderson and co-workers and by Weinberg and must be very rare.

This classification may be useful for pathologic characterization but it has limited clinical value. Hemodynamically and angiographically the muscular, membranous, and valvular types are indistinguishable from each other. Surgical considerations for these three types are the same. The Ebstein's type may not belong to the tricuspid atresia group both on the basis of pathologic appearance and embryologic origin.[16] It also is hemodynamically indistinguishable from classic cases of tricupsid atresia but angiographically it can be distinguished. A right atrial angiogram shows the left border of the right atrial shadow to be displaced more to the left than is usual in tricuspid atresia. The most important reason why this type should be differentiated from other types of tricuspid atresia is because of the surgical implication. Whereas a palliative procedure or Fontan type of operation would be considered for other types of tricuspid atresia, excision of the imperforate Ebstein's tricuspid valve with prosthetic valve replacement is presently the procedure of choice in this type of anomaly.[13] The atrioventricular canal type is extremely rare. In summary, the important anatomic types of tricuspid atresia (with the exception of the Ebstein's type) can not be clinically distinguished from each other, nor is such identification clinically useful.

Table III Classification of tricuspid atresia based on associated anatomic defects*

Type I Normally related great arteries
 a Pulmonary atresia and intact ventricular septum
 b Pulmonary hypoplasia and small ventricular septal defect
 c No pulmonary hypoplasia and large ventricular septal defect
Type II D-transposition of the great arteries
 a Pulmonary atresia with ventricular septal defect
 b Pulmonary stenosis with ventricular septal defect
 c Normal or large pulmonary artery with ventricular septal defect
Type III L-transposition of the great arteries
 a Pulmonary or subpulmonary stenosis
 b Subaortic stenosis

*Modified from Kuhne, Edwards and Burchell, Keith et al, Diehl et al, and Rosenthal

II Classification based on the roentgenographic appearance of pulmonary vascular markings

Astley and co-workers proposed a classification of tricupsid atresia based solely on the x-ray appearance of pulmonary vascular markings. Two groups were identified: (A) Decreased pulmonary vascular markings and (B) Normal or increased pulmonary vascular markings. A similar classification based on the pulmonary blood flow was used by Gasul and collaborators but they further divided each group on the basis of associated cardiac defects. Often there is progressive diminution in pulmonary blood flow with increasing age. Dick and associates[18] added a third group to Astley's classification: Group C—transition from increased to decreased pulmonary vascular markings in serial x-rays. This classification is listed in Table II. Although the principles of this classification are sound and the classification has some clinical value, it bypasses the anatomic groups (to be discussed). With the need for obtaining precise physiologic and anatomic details from cardiac catheterization and angiography prior to surgical intervention, classification by radiographic pulmonary vascular markings is inadequate for clinical use.

III Classification based on associated anatomic defects

A classification based on the interrelation hip of the great arteries was first proposed by Kuhne in 1906[a] and was later expanded by Edwards and Burchell This classification was refined and popularized by Keith and associates Thi or a slight modification of it is the most commonly used classification A classification derived from several of these sources is listed in Table III The designation of Types I or III was based on the interrelationship of the great arteries

Type I Normally related great arteries

Type II D transposition of the great art

Type III L transposition of the great arteries

Further subdivision of Type I and II is largely dependent upon the status of the pulmonary arteries (a) pulmonary atr pulmonary hypoplasia and (c) no pulmonary hypoplasia In Type I cases (normally related great arteries) the ventricular septal defect is absent (intact ventricular septum) in subgroup a small in subgroup b or large in subgroup c In type II (D transposition of the great arteries) large sized ventricular septal defect was to be present in all subgroups In contradistinction to the subgrouping of Types I and II Type III (L transposition of the great arteries) was not subdivided on the basis of pulmonary arteries These subgroups were (a) pulmonary or subpulmonary stenosis and (b) aortic steno sis[31] The inconsistency in subgrouping of the three types is apparent Furthermore conotruncal anomalies other than D and L-transposition such as double outlet right or left ventricle and truncus arteriosus can occur with tricuspid atresia Keith and associates classification does not take the great vessel anomalies other than D or L transposition into account albeit they are few in number

Tandon and Edwards analyzed 45 pathologic specimens and classified tricupsid atresia based on positional abnormalities of the great arteries (Table IV) Apart from the criticism of this paper offered by Anderson and associates one might note that they included both L transposition (ventricular inversion) and L malposition (L relationship of great arteries without ventricular inversion or isolated bulbar inversion) into a

Table IV Classification of tricuspid atresia by Tandon and Edwards

I Normally related great vessels
Group a Pulmonary atresia
Group b Pulmonary or subpulmonary stenosis
Group c No pulmonary stenosis
II Transposition of the great vessels
A Single conus
1 Noninverted great vessel
Group a Pulmonary atresia
Group b Pulmonary or subpulmonary stenosis
Group c No pulmonary stenosis
II Inverted great vessels
Group a Pulmonary atresia
Group b Pulmonary or subpulmonary stenosis
Group c No pulmonary stenosis
B Double conus
Group a Pulmonary atresia
Group b Pulmonary or subpulmonary stenosis
Group c No pulmonary stenosis
III Persistent truncus arteriosus

Reproduced with permission from the authors and publisher

Table V Classification of tricuspid atresia based on ventriculoarterial connections by Anderson et al

Normal relations
B L malposition
C D transposition
D L transposition
E Double-outlet chamber
F Persistent truncus arteriosus

Reproduced with permission from the authors and publisher

subgroup of their Type II and named them L transposition Additionally this classification is complex and difficult to follow and presumably this is the reason for its not being included in recent textbooks of Pediatric Cardiology[3, 34] The great vessel anomalies were classified in an entirely different manner by Anderson and colleagues (Table V) Therefore it is important that we have a unified classification so as to include all variations in the anatomy of the great vessels and to maintain uniformity of subgrouping Accordingly the following classification is proposed The primary grouping continues to be based on positional abnormalities of the great arteries as follows

Type I Normally related great arteries

Type II D transposition of the great arteries

Table VI A new classification of tricuspid atresia

Type I Normally related great arteries	
Type II D transposition of the great arteries	Each Type and Subtype are divided
Type III Malpositions of the great arteries other than D transposition	Subgroup a Pulmonary atresia
Subtype 1 L-transposition of the great arteries	Subgroup b Pulmonary stenosis or hypoplasia
Subtype 2 Double outlet right ventricle	Subgroup c Normal pulmonary arteries (no pulmonary stenosis)
Subtype 3 Double outlet left ventricle	
Subtype 4 D malposition of the great arteries (anatomically corrected malposition)	
Subtype 5 L malposition of the great arteries (anatomically corrected malposition)	
Type IV Persistent truncus arteriosus	

Type III Malpositions of the great arteries other than D transpositions

Type IV Persistent truncus arteriosus

Note that each type is identified with a Roman number The Type I and II are the same as in the original classification put forward by Kuhne by Edwards and Burchell and by Keith and associates Type III is different from that proposed by Keith and associates in that all malpositions of the great arteries with the exception of D transposition are included instead of only L transposition The reason for the inclusion of all malposition with the exception of D transposition is because of the rarity of these abnormalities in association with tricuspid atresia However there are many types of great vessel abnormalities and these can be further divided into subtypes

Subtype 1 L transposition

Subtype 2 Double outlet right ventricle

Subtype 3 Double outlet left ventricle

Subtype 4 D malposition (anatomically corrected malposition)

Subtype 5 L malposition (anatomically corrected malposition)

Only the great vessel anomalies that have thus far been reported in association with tricuspid atresia have been included As more positional anomalies of the great arteries (e g A transposition and A malposition) in association with tricuspid atresia are reported new subtypes to Type III may be added Note that each subtype is indicated by an Arabic number Type IV is reserved for cases of tricuspid atresia with truncus arteriosus The major types (I to IV) including the subtypes of Type III may be subdivided into

Subgroup a Pulmonary atresia

Subgroup b Pulmonary stenosis or hypoplasia

Subgroup c Normal pulmonary arteries (No pulmonary hypoplasia)

Note that each subgroup is indicated by a lower case letter

The inclusion of the status of the interventricular septum i e intact septum small or large ventricular septal defect within each subgroup has been attempted by others (Table III) However it may be advisable not to consider the status of the interventricular septum for the purpose of classification into subgroup a b and c A case we previously reported was of Type I with pulmonary atresia but had a good size ventricular septal defect Because it did not fit into any of the then existing classifications (subgroups) we proposed a new subgroup d It is probably more appropriate to retract that suggestion and approach the problem in a different manner After classifying tricuspid atresia into major Types I II III or IV (and into subtypes if it was type III) on the basis of great artery relationship and then into subgroups a b or c on the basis of pulmonary arteries (atretic stenotic or normal) one may then simply state the status of the ventricular septum—i e intact small or large ventricular septal defect or multiple ventricular septal defects for any given case Thus the above referenced case would be described as Type Ia with large ventricular septal defect The a b or c subgrouping could be carried through each major type (or subtype) The status of the interatrial septum and other associated malformations like aortic or subaortic stenosis patent ductus arteriosus persistent left superior vena cava coarctation of aorta or anomalous pulmonary venous return if present could then be

stated for each case A unified classification based on these principles is presented in Table VI This classification is simple and maintains uniformity in subgrouping but at the same time takes into account all variations in great artery anatomy that have been described in association with tricuspid atresia Should new anomalies come to light in the future this classification may easily be expanded It also preserves the basic principles of classification outlined by Kuhne[6] by Edwards and Burchell[7] and by Keith Rowe and Vlad[8] so that this can easily be adopted by cardiologists surgeons and pathologists This classification also follows the terminology of congenital heart disease proposed and reemphasized by Van Praagh[3] with regard to the conotruncal anatomy One could easily include the remaining segmental subsets, namely visceroatrial situs and ventricular loop and describe each case by the notations [(S D S) (S D D) (S D L) and so on] as the case may be[1 39]

In summary tricuspid atresia has been classified on the basis of morphology of the atretic tricuspid valve x ray appearance of pulmonary vascular markings and associated cardiac defects The limited clinical usefulness of the first two types of classifications has been pointed out and it is suggested that anatomic classifications based on the associated defects is more useful Recent advances in corrective surgery demand that we know the exact anatomy Additionally this information necessary for classifications is usually available after catheterization and angiography studies prior to palliative or corrective surgery It is recommended that anatomic classification based on the associated defects as proposed here (Table VI) be adopted for general use

Bruce S Alpert M D Wesley Covitz M D Martin J Frank M D William B Strong M D and Paul M Weinberg M D provided critical review of the manuscript

REFERENCES

1 Fontan F., and Baudet E Surgical repair of tricuspid atresia, Thorax 26 240 1971
2. Kreutzer A., Bono H Galindez, E de Palma C and Laura J P An operation for correction of tricuspid atresia American College of Surgeons Atlantic City October November 1971
3 Rao P S (Moderator) Malm J R and Miller R A Symposium on "Tricuspid Atresia Program for Scientific Sessions of Section on Cardiology 46th Annual Meeting of the American A ademy of Pediatrics, Nov 5-10 1977 New York City N Y
4 Van Praagh R Ando M and Dungan, W T Anatomic types of tricuspid atresia Clinical and developmental implications (Abstract) Circulation 44(Suppl. II) 115 1971
5 Astley R., Oldham J S., and Parson C Congenital tricuspid atresia Br Heart J 15 287 1953
6. Kuhne M Uber Zwei Falle Kongenitaler Atresie des Ostium Venosum Dextrum Jahresb Kinderh. 63 225 1906
7 Edwards, J E., and Burchell, H B Congenital tricuspid atresia A classification Med. Clin North Am 33 1117 1949
8 Keith, J D., Rowe R D and Vlad, P Heart Disease in Infancy and Childhood, New York, 1958 Macmillan Publishing Co., Inc., pp 434-470
9 Hennette Rapport au Sujet d une note de M le docteur Hennette sur un Cas de cyanose generale Liee á un vice congenitale du coeur par M Van Kempen Gaz Méd. Paris 16 618, 1861
10 Kelly C Malformation of the heart in a case of cyanosis Tr Path Soc London 19 1851 1868
11 Elster S K Congenital atresia of pulmonary and tricuspid valves, Am J Dis. Child. 79 692 1950
12 Chiche P Etude anatomique et clinique des atresies tricuspidiennes, Arch. Mal. Coeur 44 981 1952
13 Van Praagh R Discussion after paper by Vlad P Pulmonary atresia with intact ventricular septum in Barrett Boyes, B G., Neutze J M., and Harris, E A eds Heart Disease in Infancy Diagnosis and Surgical Treatment London 1973 Churchill Livingstone pp 246-7
14 Weinberg P M Anatomy of tricuspid atresia and its relevance to current forms of surgical therapy Ann. Thorac Surg (In press)
15 Anderson R. J., Wilkinson J L., Gerlis, L. M., Smith A., and Becker A E Atresia of the right atrioventricular orifice Br Heart J 39 414 1977
16 Rao P S Jue K L Isabel-Jones, J and Ruttenberg H D Ebstein s malformation of the tricuspid valve with atresia Differentiation from isolated tricuspid atresia, Am J Cardiol. 32 1004 1973
17 Fontana R S., and Edwards, J E Congenital cardiac disease A review of 357 cases studied pathologically Philadelphia 1962 W B Saunders Company p 39
18 Lev M Liberthson R. R., Joseph, R H., Seten, C E., Kun ke R D Eckner F A. O., and Miller R. A. The pathologic anatomy of Ebstein s disease Arch. Pathol. 90.334 1970
19 Kumar A. E Flyer D C., Miettinen O S., and Nadas, A S Ebstein s anomaly Clinical profile and natural history Am J Cardiol 28 84 1971
20 Miller R A. Discussion of paper by Van Praagh, R., Ando M and Dungan W T Circulation 44(Suppl. II) 115 1971
21 Gerlis, L. M and Anderson R. H Cor triatriatum dexter with imperforate Ebstein s anomaly Br Heart J 38 108 1976
22 Gasul, B M Arcilla, R A., and Lev M Heart Disease in Children Diagnosis and Treatment Philadelphia 1966, J B Lippincott, Co., pp 656-685
23 Gallaher M E., and Fyler D C Observations in changing hemodynamics in tricuspid atresia without associated transposition of the great vessels, Circulation 35 381 1967
24 Dolara A., Fazzini, P F., Marchi, F., and Tordini, B Changing clinical features in tricuspid atresia without transposition of the great vessels Report of two cases, Acta Cardiol (Brux) 24 2 5 1969
25 Marcano B A Riemenschneider T A., Ruttenberg H

D., Goldberg S J and Gyepes M Tricuspid atresia with increased pulmonary blood flow An analysis of 13 cases Circulation 40 399 1969
26 Cabriele O F Progressive obstruction of pulmonary blood flow in tricuspid atresia J Thorac Cardiovasc Surg 59 447 1970
27 Rao P S and Sissman N J Spontaneous closure of physiologically advantageous ventricular septal defects Circulation 43 83 1971
28 Rao P S Linde L M Liebman J and Perrin E Functional closure of physiologically advantageous ventricular septal defects Observation in three cases with tricuspid atresia Am J Dis Child 127 36 1974
29 Rao P S Natural history of the ventricular septal defect in tricuspid atresia and its surgical implications Br Heart J 39 276 1977
30 Dick, M Fyler D C and Nadas, A S Tricuspid atresia Clinical course in 101 patients Am J Cardiol. 36 327 1975
31 Keith J D Rowe R D and Vlad P Heart Disease in Infancy and Childhood 2nd ed New York 1966 Macmillan Publishing Co Inc pp 664 681
32 Vlad P Tricuspid Atresia *in* Keith J D Rowe R D and Vlad P ed Heart Disease in Infancy and Childhood 3rd ed New York 1977 Macmillan Publishing Co Inc pp 518-541
33 Diehl A M Lauer R M and Shanker K R. Tricuspid atresia *in* Moss, A J., and Adams, F H eds. Heart Disease in Infants Children and Adolescents, Baltimore, 1968 The Williams & Wilkins Company pp 517-526
34 Paul M H Tricuspid atresia *in* Watson H ed. Pediatric Cardiology St Louis 1968 The C V Mosby Company pp 451-467
35 Nadas, A S and Fyler D C Pediatric Cardiology 3rd ed Philadelphia 1972 W B Saunders Company pp 588-597
36 Rosenthal A Tricuspid atresia *in* Moss A J Adams, F H., and Emmanouilides G C., eds Baltimore 1977 The Williams & Wilkins Company pp 289-301
37 Perloff J K The Clinical Recognition of Congenital Heart Disease 2nd ed Philadelphia 1978 W B Saunders Company pp 619-640
38 Tandon R., and Edwards J E Tricuspid atresia A re-evaluation and classification J Thorac Cardiovasc. Surg 67 530 1974
39 Van Praagh R Terminology of congenital heart disease Glossary and commentary Circulation 56 139 1977

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

Calcium antagonists

Thomas T Zsotér M D F R C P (C) F A C P
Toronto Ontario Canada

Calcium antagonists represent a new class of drugs of considerable theoretical and practical importance Most of the drugs grouped together under such name are not available on the market in North America but many clinical trials suggest that they are valuable in the treatment of various cardiovascular abnormalities

Calcium antagonists as implied by the name interfere with the normal function of Ca in the body including that in the excitation-contraction coupling in smooth muscle and in cardiac muscle Their effect according to Fleckenstein[1] is explained by a selective blockade of the slow channel of the cell membrane—i e by interference with the transmembrane Ca^{2} influx Our own research suggests that other sites of action are also important

Calcium ions are recognized as playing an important role in the contractile process of the heart smooth muscle and skeletal muscle in glandular secretion and in the release of neurotransmitters In view of this it is rather surprising that calcium antagonists can be used therapeutically having apparently a rather selective action on the cardiovascular system without important side effects

Diagrammatic presentation

Fig 1 lists the drugs grouped together as calcium antagonists by Fleckenstein Besides these agents of variable chemical structure several other drugs are known to interfere with the availability of Ca^{2} for contraction of smooth muscle The relaxant effect of diazoxide nitroglycerin papaverine and hydralazine depend to a great extent on the extracellular calcium concentration and their action just like that of drugs listed in Fig 1 is diminished in the presence of extra Ca in the tissue bath Sodium nitroprusside another direct acting vasodilator was found to result in a dose related increase of calcium efflux from vascular strips[2] There is an important difference however between the pharmacological action of other smooth muscle relaxants and calcium antagonists namely that depression of cardiac contractility is characteristic only for the latter drugs[1, 3]

Mechanism of action

The basic mechanism of action of calcium antagonists more precisely the exact site of their action is not yet clarified In isolated cardiac muscle depression of contractility could be demonstrated without any alteration in the upstroke velocity of the action potential only with slight abbreviation of the plateau phase From these experiments and others demonstrating an effect on the action potential after Na flux was inhibited, Fleckenstein concluded that calcium antagonists act by selective inhibition of the calcium influx through the cell membrane If this mechanism would be the only explanation for their action calcium antagonists should inhibit ⁴Ca uptake by the cells when measured with the lanthanum methods[5] However in our experiments exposure of electrically driven rat atrium to verapamil nifedipine or diltiazem in concentrations which depress cardiac contractions did not cause any diminution in uptake of lanthanum resistant Ca Similarly calcium antagonists failed to reduce uptake of lanthanum resistant calcium in rabbit mesenteric vein of rat aorta This was so even in vessels in which calcium influx was enhanced by exposure to 60 mM K [6]

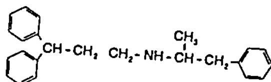
From the Departments of Medicine and Pharmacology University of Toronto Toronto, Ontario Canada

Received for publication Jan 31 1979

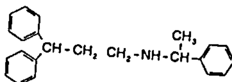
Reprint requests Dr T T Zsotér Dept of Pharmacology University of Toronto Toronto Ontario M5S 1A8 Canada

0002-8703/80/060805 + 06$00 60 0 © 1980 The C V Mosby Co

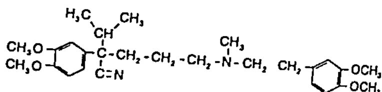
Prenylamine



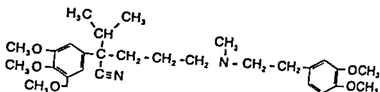
Fendiline



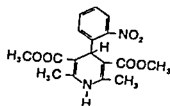
Verapamil



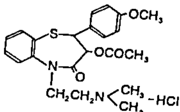
D-600 =
Methoxyverapamil



Nifedipine



Diltiazem



Perhexiline

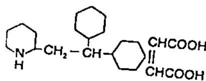


Fig Calcium antagonistic drugs and their structures

On the basis of these and other experiments on ⁴⁵Ca efflux[6] as well as reports of other authors[7, 8] we conclude that calcium antagonists must act on other sites as well as the cell membrane. We postulate that these agents interfere with the availability of Ca^{2+} for contraction of vascular smooth muscle and cardiac muscle mainly intracellularly by inhibiting the release of Ca^{2+} from various pools.

Pharmacology

The effect of calcium antagonists on the smooth muscle in vessels and other tissues is similar to that of the direct acting vasodilators such as hydralazine, diazoxide, nitrites, etc. The relaxation of smooth muscle and the prevention of norepinephrine, angiotensin, methacholine, K or barium chloride induced contractions is not mediated through any specific action on alpha or beta adrenergic or cholinergic receptors.[1, 9] Ca antagonists increase blood flow not only in coronary but also in mesenteric, renal and femoral vessels.[10, 1] Many studies indicate blood pressure lowering in animals as well as in man.[1, 5] Various calcium antagonists consistently were found to decrease systemic vascular resistance.[11] In addition, pulmonary arterial pressure was reported to be lowered.[17]

The cardiac effect of calcium antagonists in vitro is different from that in vivo. In isolated papillary muscle or in other in vitro preparations they cause a dose-related depression of cardiac contractions and dp/dt.[4] In this respect the effect was nifedipine greater than verapamil which in turn was greater than diltiazem.[1] In vivo, however, the decrease in blood pressure activates baroreceptor reflexes with consequent increase in contractility (as measured by max dp/dt, ejection fraction, or decreased left ventricular end-diastolic pressure) and heart rate resulting in higher cardiac output when calcium antagonists are given in therapeutic doses. Consequently in vivo one can not expect the higher coronary blood flow to be associated with lower myocardial oxygen uptake as found in isolated heart preparations.[1] Calcium antagonists were reported to protect the myocardium from ischemia induced changes by enhancing coronary blood flow and also by other mechanisms.[23] Furthermore, reduction of infarct size after coronary ligation and enhanced development of collateral circulation was claimed by some studies.

Table I Clinical indications

Angina pectoris
Variant angina
Arrhythmia
Hypertension
Hypertensive crisis
Hypertrophic cardiomyopathy
? Chronic refractory heart failure

Antiarrhythmic properties of verapamil and diltiazem were demonstrated against arrhythmias induced by various methods such as ouabain, chloroform-epinephrine and coronary ligation.[26, 2] Slowing the AV conduction and increasing the refractory period of the AV node were suggested as the principal mechanism for the antiarrhythmic effect.

Diltiazem was found to increase sodium diuresis to a greater extent than was explained by its effect on enhancing renal blood flow.[28] Such an action, if confirmed, could mean an important advantage over other drugs used in treatment of angina pectoris or hypertension. At present there is little or no evidence that calcium antagonists would have any other significant pharmacological effect than those mentioned above.

Studies on pharmacokinetics of verapamil indicate an almost complete oral absorption and a rapid biotransformation of the drug.[29, 30] First pass metabolism in the liver must be quite significant, as the bioavailability of oral doses is reduced to 10 to 22%. Information on pharmacokinetics of other calcium antagonists is far from being adequate.

Therapeutic use

Table I lists clinical situations where calcium antagonists may be of value.

Most of the clinical studies were concerned with the use of calcium antagonists in angina pectoris. The fact that these drugs increase coronary blood flow, decrease arterial pressure and have an antiarrhythmic effect would suggest their value as antianginal agents. Furthermore, in contrast to propranolol, these drugs could also be used in patients with bronchospasm. In addition to uncontrolled clinical trials there were some double blind studies which indicated these drugs superior to placebo in reducing the number of daily attacks, in necessitating less nitroglycerin consumption and in improvement of exercise

tolerance[31,3] These effects were reported when verapamil was given in doses of 80 mg three times a day or more[31,32] nifedipine 10 mg four times a day[31] and perhexiline 200 mg twice a day[34] Others using the same or lower doses of verapamil or nifedipine failed to observe significant improvement over placebo treatment None of the studies has proven superiority of calcium antagonists over propranolol in the prevention of anginal attacks[31,3]

The most convincing results with calcium antagonists were obtained in variant angina Several authors reported that patients treated with verapamil nifedipine or diltiazem became symptom free or markedly improved and attacks associated with ST elevation in the electrocardiogram occur much less frequently[35,8] The largest series was that of Hosada and Kimura[35] who found that 30 of 47 patients with variant angina became symptom free while on nifedipine[35] Thus calcium antagonists seem clearly superior to propranolol in the treatment of Prinzmetal s variant angina but not of effort angina The effectiveness of calcium antagonists in variant angina can be explained by the ability to prevent coronary vasospasm

Clinical experience in the treatment of arrhythmia is confined mainly to verapamil given intra nously This drug was shown in several studies) be effective in causing the termination of roxysmal supraventricular tachycardia when given intravenously and in preventing the recurrence of attacks when given orally[27,3] In ventricular arrhythmias however verapamil was less effective As to atrial fibrillation in one study intravenous verapamil reduced the ventricular rate in 111 of 115 patients but converted the fibrillation to sinus rhythm in only one patient[39] More experience is required before we may conclude about the effectiveness of various calcium antagonistic drugs in the treatment of arrhythmias

Hemodynamic evaluation both in animal and human experiments consistently demonstrated that calcium antagonists cause a dose related decrease of systolic and diastolic pressure In view of these results the scarcity of controlled clinical trials to investigate the value of these agents in the treatment of hypertension is rather surprising This is particularly true when considering that in vessels of spontaneously hypertensive rats abnormal Ca^{2} handling was demonstrated suggesting the possibility that calcium antagonists might offer a more logical treatment of hypertension than other vasodilators[40,41] Guazzi and colleagues[41] reported a pronounced decline of arterial pressure after oral or sublingual nifedipine in patients with severe hypertension including three with hypertensive encephalopathy[14] The prompt onset of action described by these and by other authors[14] suggests that this drug might be of great value in the treatment of hypertension emergencies Aoki and others observed a significant lowering of systolic and diastolic pressure of long duration in hypertensive patients a single dose of 30 mg nifedipine remained effective during a 10 hour long observation period

Hypertrophic cardiomyopathy may be another indication for the use of calcium antagonists as verapamil was reported to improve exercise capacity in these patients[2] There is no evidence however that these drugs would be useful in the treatment of refractory heart failure As nifedipine has no venodilator effect[43] and there is no indication that other calcium antagonists would have either they are unlikely to be as effective as nitrites or sodium nitroprusside in reducing cardiac preload

Side effects

Side effects mostly headache and dizziness were reported in 9% of 8 072 patients treated with verapamil[30] Side effects with nifedipine were encountered in 17% of 5 008 patients but they were usually only minor occurrences such as headache heat sensation vomiting or nausea[44] Perhexiline was found to cause side effects quite frequently[3]

REFERENCES

1 Fleckenstein A Specific
myocardium cardiac pac
muscle Ann Rev Pharm
2 Zsotér T T Henein
effe t of sodium nit
Ca from rabbit an
1977
3 Nayler W C a
contractility oxv
ability in mam
6 120 1972
4 Nakajima N H
moto A Effect
ical activity of
guinea pig Jap

5 Van Breemen C Farinas B R Casteels R Gerba P Wuytack F and Deth R Factors controlling cytoplasmic Ca concentration Phil Trans R Soc London B 265 57 1973
6 Church J and Zsotér T Can J Physiol Pharmacol (In press)
7 Bayer R Mennekes R Kaufmann R and Mannhold R Inotropic and electrophysiological actions of verapamil and D600 in mammalian myocardium Naunyn Schmiedebergs Arch Pharmacol 290 49 1975
8 Ito Y Kuriyama K and Suzuki K The effects of diltiazem (CRD-401) on the membrane and mechanical properties of vascular smooth muscles of the rabbit Br J Pharmacol 64 503 1978
9 Nagao T Sato M Iwasawa Y Takada T Ishida R Nakajima K and Kiyomoto A Studies on a new 1,5 benzothiazepine derivative (CRD-401) Jap J Pharmacol 22 467 1972
10 Yamagushi I Ikezewa K Takada T and Kiyomoto A Studies on a new 1 5 benzothiazepine derivative (CRD-401) Effects of renal blood flow and renal function Jap J Pharmacol 24 511 1974
11 Vater W and Schlossmann K Effects of nifedipine on the haemodynamics and the oxygen consumption of the heart in animal experiments *in* Jatene A D and Lichtlen P R Third International Adalat Symposium Amsterdam 1976 Excerpta Medica p 33
12 Himori N Ono H and Taira N Simultaneous assessment of effects of coronary vasodilators on the coronary blood flow and the myocardial contractility by using the blood perfused canine papillary muscle Jap J Pharmacol 26 427 1976
13 Sato M Nagao T Yamaguchi I Nakajima K and Kiyomoto A Pharmacological studies on a new 1,5 benzothiazepine derivative (CRD-401) Arzneim Forsch 21 1338 1971
14 Guazzi M Olivari M T Polese A Fiorentini C Magrini F and Moruzzi P Nifedipine a new antihypertensive with rapid action Clin Pharmacol Ther 22 528 1977
15 Aoki K Kondo S Mochizuki A Yoshida T Kato D Kato K and Takikawa K Antihypertensive effect of cardiovascular Ca antagonist in hypertensive patients in the absence and presence of beta adrenergic blockade AM HEART J 96 218 1978
16 Kowajima I Ueda K Kamata C Matsushita S Kuramoto K Murakami M and Hada Y A study on the effects of nifedipine in hypertensive crises and severe hypertension Jap Heart J 19 455 1978
17 Landmark K Refsum A M Simonson S and Storstein O Verapamil and pulmonary hypertension Acta Med Scand 204 299 1978
18 Nabata K Effects of calcium antagonistic coronary vasodilators on myocardial contractility and membrane potentials Jap J Pharmacol 27 239 1977
19 Murakami M Murakami E and Takekoshi N Antihypertensive effect of (4 2 nitrophenyl) 2 6 dimethyl 1 4-dihydropyridine 3 5 dicarbonic acid dimethylester (Nifedipine Bay—a 1040) A new coronary dilator Jap Heart J 13 128 1972
20 Fleckenstein A Die Zugelung des Myocard Stoffwechselung durch Verapamil Arzneim Forsch 20 1317 1970
21 Henry P D Protection of ischemic myocardium by nifedipine *in* Jatane A D and Lichtlen P R Third International Adalat Symposium Amsterdam 1976 Excerpta Medica p 55
22 Bier C Klassen G Huttner I Marner D Mogensen L and Zborowska Sluis D Mitochondrial protection by nifedipine in ischemic myocardium Circulation 57 and 58 (Suppl II) II 99 1978
23 Clark R E Christlieb I Y Henry P D Fischer A E Nora J D Williamson J R and Sobel B A Nifedipine a myocardial protective agent Am J Cardiol 44 825 1979
24 Schmier J Brückner V B Mittmann V and Wirth R K Intercoronary collaterals and intramyocardial blood distribution in dogs following nifedipine administration compared with controls *in* Jatane A D and Lichtlen P R Third International Adalat Symposium Amsterdam 1976 Excerpta Medica p 42
25 Reimer K A Lowe F E and Jennings R E Effect of the calcium antagonist verapamil on necrosis following temporary coronary artery occlusion in dogs Circulation 55 581 1977
26 Yamada K Shimamura T and Nakajima K Studies on a new 1,5 benzothiazepine derivative (CRD-401) Antiarrhythmic actions Jap J Pharmacol 23 321 1973
27 Krikler D M Verapamil in cardiology Eur J Cardiol 2 3 1974
28 Kinoshita M Kushukawa R Shimono Y Motomura M Tomonaga G and Hoshino T Effects of diltiazem hydrochloride on renal hemodynamics and urinary electrolyte excretion Jap Circ J 42 553 1978
29 Schomerus M Spiegelhalder B Stieren B and Eichelbaum M Physiological disposition of verapamil in man Cardiovasc Res 10 605 1976
30 Singh B N Ellrodt G and Peter C T Verapamil A review of its pharmacological properties and therapeutic use Drugs 15 169 1978
31 Sandler G Clayton G A and Thornicroft S G Clinical evaluation of verapamil in angina pectoris Br Med J 3 224 1968
32 Livesley B Catley P F Campbell R C and Oram S Double blind evaluation of verapamil propranolol and isosorbide dinitrate against a placebo in the treatment of angina pectoris Br Med J 1 375 1973
33 Menna F Traina M Ferreiros E and Cassera F C Long term double blind cross over study on the antianginal efficacy of Adalat compared with placebo *in* Jatene A D and Lichtlen P R Third International Adalat Symposium Amsterdam 1976 Excerpta Medica p 272
34 Mir M A and Kafetzakis E M *Assessment of perhexiline maleate* in angiographically proven intractable angina A double blind trial AM HEART J 96 350 1978
35 Hosada S and Kimura E Efficacy of nifedipine in the variant form of angina pectoris *in* Jatene A D and Lichtlen P R Third International Adalat Symposium Amsterdam 1976 Excerpta Medica p 195
36 Parodi O Simonetti I and Maseri A Management of crescendo angina by verapamil A double blind cross over study in CCU Circulation 55 and 56(Suppl III) III 224 1977
37 Yasue K Nagao M Omote S Takizawa A Miwa K and Tanaka S Coronary arterial spasm and Prinzmetal s variant form of angina induced by hyperventilation and Tris buffer infusion Circulation 58 56 1978
38 Heupler F A and Proudfit W C Nifedipine therapy for refractory coronary arterial spasm Am J Cardiol 44 798 1979
39 Schamroth L Krikler D M and Garrett G Immediate effects of intravenous verapamil in cardiac arrhythmias Br Med J 1 660 1972
40 Wei Kiann W U Janis R A and Daniel E E

Calcium accumulation and enzymatic activities of subcellular fractions from aortas and ventricles of genetically hypertensive rats Circ Res 39 353 1977
41 Zsotér T T., Wolchinsky C., Henein N F., and Ho L. C Calcium kinetics in the aorta of spontaneously hypertensive rats Cardiovasc Res 11 353 1977
42 Rosing D R Kenneth M Maron B J and Epstein S E Verapamil therapy a new approach to the pharmacologic treatment of hypertrophic cardiomyopathy II Circulation 60 1208 1979
43 Mostbeck, A Partsch K., and Perschl L. Extracardial effects of nifedipine Measurements of liver blood flow in animals and humans and of peripheral circulation in the lower limbs, *in* Hashimoto K., Kimura E., and Kobayashi T First International Nifedipine "Adalat" Symposium Tokyo 1975 University of Tokyo Press p 1.6
44 Ebner F., and Dünschede H B Haemodynamics, therapeutic mechanism of action and clinical findings of Adalat use based on worldwide clinical trials, *in* Jatene A. D and Lichtlen P R Third International Adalat Symposium Amsterdam 1976 Excerpta Medica p 283

Exercise testing for the diagnosis of coronary artery disease

The exercise test has been the standard noninvasive test to help confirm or exclude the diagnosis of coronary artery disease The time honored criterion for myocardial ischemia is ST segment depression which although being an electrophysiological abnormality has been most often correlated with findings at coronary arteriography which then confirm an anatomic abnormality Recognizing the limitations of coronary arteriography itself to diagnose coronary disease and the fact that myocardial ischemia may be present without the presence of coronary disease (such as in patients with valvular heart disease or hypertension) most previous studies have demonstrated that the presence of an abnormal ST segment response to stress almost always correctly predicted the presence of coronary artery disease However these studies largely consisted of males referred to the catheterization laboratory for chest pain complaints who would be expected *to have a high pre test (exercise) risk of coronary disease* Recently some reports have demonstrated that when patients with a low pre test risk such as asymptomatic men or women with atypical chest pain have been subjected to exercise testing and subsequent coronary arteriography a disturbingly high rate of false positive exercise tests has resulted although most reported series dealt with small numbers of patients.

In order to evaluate how much additional information analysis of the ST segment response to exercise could yield for the prediction of coronary disease beyond that which was available from a detailed description of chest pain and the sex of a patient in a large cohort of patients we recently correlated certain clinical and exercise data with coronary arteriography from the National Collaborative Study on Coronary Artery Surgery (CASS)

The patient population was derived from 15 participating centers broadly distributed throughout the United States and Canada and consisted of 1 465 men and 580 women All patients underwent graded exercise testing using the Bruce protocol and cardiac catheterization The exercise test was considered positive when there was ≥ 1 mm. of ST segment depression or elevation Significant coronary artery disease was defined as ≥ 70% narrowing of the diameter of at least one major coronary vessel. The chest pain complaints of the patients were categorized into three groups definite angina probable angina and nonischemic chest pain Patients having prior myocardial infarction or taking digitalis at the time of the exercise test were excluded from the analysis.

The results of the study are summarized in Table I The pre-test risk of coronary disease varied from 5% to 89% depending upon the sex of the patient and the description of chest pain. A positive exercise test only increased the pre-test risk by 1% to 14% whereas a negative test lowered the risk by only 0% to 29% When the pre test risk of coronary disease was high (e g men with definite angina) a positive exercise test was highly correlated with the presence of coronary disease *although it only slightly increased an already high pre-test* likelihood of coronary disease however a negative exercise test in this subgroup was more likely to be falsely negative Conversely when the pre test risk of coronary disease was low (e g., women with nonischemic pain) a negative exercise test was highly predictive of the absence of coronary disease although again only confirming an already low pre-test likelihood of coronary disease whereas a positive exercise test in this subgroup was more likely to be falsely positive

The conclusion of this study indicates that before the results of exercise testing can be objectively evaluated the pre test risk of coronary disease must first be considered. Although the results from this study are derived from symptomatic patients the conclusion appears to support other studies showing that the percentage of false positive exercise tests among asymptomatic patients may be as high as 65%

A major limitation of the study is that only the ST segment was evaluated and there may be other exercise test variables which may prove more useful for the prediction and extent of coronary disease such as the heart rate and blood pressure

Table I Pre test risk of coronary disease and predictive value of a positive and negative exercise test in the coronary artery surgery study (CASS)

History	*Sex*	*No*	*Pre test risk of coronary disease (%)*	*Predictive value (%)*	
				*+ET**	*−ET**
Definite angina	Male	6?0	89	96	35
Definite angina	Female	98	62	73	67
Probable angina	Male	594	0	87	56
Probable angina	Female	240	40	54	78
Nonischemic pain	Male	251	22	39	86
Nonischemic pain	Female	24?	5	6	95

Predictive value of a positive exercise test (+ET) = percentage of positive results that are truly positive
Predictive value of a negative exercise test (−ET) = percentage of negative results that are truly negative

response to exercise and the amount configuration onset and duration of ST segment depression Our study should not be used to minimize the importance of exercise testing in evaluating arrhythmias confusing symptoms, responses to therapy (medical and surgical) and work capacity However when used for the diagnosis of coronary disease in the positive negative classification it appears that the results of exercise testing are limited in improving upon an estimate of the probability of coronary disease based upon the classification of chest pain and the sex of the patient

Donald A Weiner MD
Carolyn H McCabe BS
Thomas J Ryan MD
The Evans Memorial Department of Clinical Research and the Department of Medicine Boston University Medical Center Boston Mass 02118

REFERENCES

1 Roitman D Jones W B and Sheffield L T Comparison of submaximal ECG test with coronary cineangiocardiogram Ann Intern Med 72 641 1970
2 McConahay D R McCallister B D and Smith R E Postexercise electrocardiography correlations with coronary arteriography and left ventricular hemodynamics Am J Cardiol 28 1 1971
3 Martin C M and McConahay D R Maximal treadmill exercise electrocardiography correlations with coronary arteriography and cardiac hemodynamics Circulation 46 ?6 1972
4 Bartel A G Behar V S Peter R H Orgain, E S and Kong, Y Graded exercise stress tests in angiographically documented coronary artery disease Circulation 49 348 1974
5 Sketch, M H Mohiuddin S M., Lynch, L D Zencka A E and Runco V Significant sex differences in the correlation of electrocardiographic exercise testing and coronary arteriograms Am J Cardiol 36 169 1975
6 Linhart J W Laws J G., and Satinsky J D Maximum treadmill exercise electrocardiography in female patients Circulation 50 1173 1974
7 Detry J M R Kapita B M Cosyns J., Sottiaux B Brasseur L A and Rousseau M F. Diagnostic value of history and maximal exercise electrocardiography in men and women suspected of coronary heart disease Circulation 56 756 1977
8 Weiner D A., Ryan T J McCabe C H Kennedy J W., Schloss M Tristani, F., Chaitman B R and Fisher L D Exercise stress testing correlations among history of angina ST segment response and prevalence of coronary artery disease in the Coronary Artery Surgery Study (CASS) N Engl J Med 301:230 1979
9 Froelicher V F., Jr Yanowitz F G Thompson A J and Lancaster M C The correlation of coronary angiography and the electrocardiographic response to maximal treadmill testing in 76 asymptomatic men Circulation 48 597 1973
10 Borer J S Brensike J F Redwood D R Itscoitz S B Passamani E R., Stone N J Richardson, J M Levy R I and Epstein S E Limitations of the electrocardiographic response to exercise in predicting coronary artery disease N Engl. J Med 293 367 1975

The risk of coronary angiography and National Health planning

Ever since the development of selective coronary angiography physicians have been concerned about the risks of this valuable diagnostic test After the success by Sones and Shirey with low complication rates, others were initially frustrated in their attempts to duplicate their results The percutaneous femoral technique and Judkins precurved catheters made the procedure easier but may have encouraged those less prepared to try coronary angiography and complications were frequent * During the sixties as many of the major medical centers were learning the procedure frequently by self education, relatively few studies were done The success of coronary bypass surgery at the end of the decade led to an explosion in the number of hospitals doing coronary angiography Since there were few trained coronary angiographers complication rates in these medium-sized hospitals were high as physicians in these laboratories learned the painful lessons previously learned in the larger institutions

Many efforts have been made to define the optimal conditions for safety of coronary angiography It is understandable that an experienced angiographic team is necessary but the level of experience to prevent unnecessary complications has been difficult to define since the patient population is inherently at some risk regardless of the laboratory conditions. It is, perhaps, natural for those associated with major medical centers to assume that large case loads are necessary and the surveys of Adams and Abrams have often been interpreted to indicate an inverse relationship between case loads and complication rates However these surveys were done during the early seventies and probably reflect the lack of experienced angiographers in the moderate-sized laboratories. This can be surmised from the dramatic improvement in complication rates between the first and second surveys in the smallest laboratories using the femoral technique Recent surveys in our state have shown that well trained angiographers can start new laboratories and have remarkably low complication rates even when performing fewer than 150 cardiac catheterizations per laboratory per year

The Washington State experience has major implications for health planning The present National Guidelines for Health Planning tend to favor the concept of a few major

0002-8703/80/060812 + 02$00.20/0 © 1980 The C V Mosby Co.

heart centers with dedicated cardiac catheterization laboratories and accompanying cardiac surgery programs. These centers will always be important, but we should not discourage the development of regional dual purpose diagnostic laboratories. There is a need for angiographic equipment in hospitals located in large population areas surrounding major cities or distant from major cities for emergency angiographic studies. If these laboratories can also be utilized for coronary angiography as they are in the State of Washington the utilization of this expensive equipment is significantly improved and there is better patient access to this valuable diagnostic test.

The existing National Guidelines for Health Planning were established in spite of the absence of studies to indicate that these guidelines would improve on either the safety or the cost of cardiac catheterization or cardiac surgery. These cardiac catheterization guidelines are inappropriate because they represent an attempt to set numerical standards based on outdated opinions and data. Medicine has always been a dynamic profession and it is time to accept the fact that the optimal conditions for coronary angiography and cardiac surgery have changed. If health planners must have guidelines let us at least base such guidelines on objective data and leave them flexible enough to adapt to changing circumstances and local health care needs.

Charles E Hansing M D F.A.C.C.
Overlake Memorial Hospital
Bellevue Wash
Department of Medicine
University of Washington
Seattle Wash

REFERENCES

1. Sones F M Jr and Shirey E K Cine coronary arteriography Mod. Concepts Cardiovasc Dis 31 375 1962
2. Ross R S and Gorlin R Cooperative study on cardiac catheterization Coronary arteriography Circulation 37(Suppl.) III 67 1968
3. Judkins, M P Selective coronary angiography Radiology 89 815 1967
4. Lage H L and Campbell W B Percutaneous tran femoral coronary arteriography prevention of morbid complications Chest 67 ??1 1975
5. Takaro T Hultgren H Littmann D Wright E and Oteen N An analysis of deaths occurring in association with coronary arteriography AM HEART J 86 587 1973
6. Gau G T Oakley C M., Rahimtoola S Raphael M and Steiner R Selective coronary arteriography a review of 18 months experience Clin Radiol 21 275 1970
7. Adams, D F Fraser D B and Abrams H L The complications of coronary arteriography Circulation 48 609 1973
8. Abrams H L and Adams D F The complications of coronary arteriography Circulation Abstracts of the 48th Scientific Sessions II 27 1975
9. Optimal resources for examination of the chest and cardiovascular system Report of the Inter Society Commission for Heart Disease Resources Circulation 53 A 1 1976
10. Hansing C E Hammermeister K., Prindle K Twiss, R., Schwindt R., Gowing B Crecelaius, L., and Robinson W Cardiac catheterization experience in hospitals without cardiovascular surgery programs Cathet Cardiovasc Diag 3 ?07 1977
11. Hansing C E The risk and cost of coronary angiography J.A.M.A 24/31 731 1979
12. National Guidelines for Health Planning publication No HRA 78-643 U.S Dept of Health Education and Welfare 1978
13. Optimal criteria for care of heart patients Heart Disease Advisory Committee of the Joint Commission on Accreditation of Hospitals J.A.M.A 226 1340 1973

Bladder trauma from jogging

The current popularity of jogging is bound to throw up its share of traumatic complications like any other sporting activity. One of these has been hematuria either microscopic or macroscopic. While strenuous exertion may give rise to rhabdomyolysis and myoglobinuria the more restrained exercise of jogging may be less likely to produce these symptoms. Neither is there the likelihood of the generalized splanchnic vasoconstriction of extreme exertion and the resultant ischemic renal injury.

On the other hand the rhythmic relaxed style of the jogger favors the circumstances which can provoke the bladder lesion I have observed in a number of long distance runners. I have only found these in men and the hematuria which was profuse in some occurred on the first occasion of urination following the running event. The discoloration of the urine usually disappeared within 24 hours. Sometimes small clots were passed and there was dull suprapubic pain with dysuria. The episode was either an isolated or an occasional event.

Cystoscopy within the first few days of the symptom shows well-defined localized contusions on the posterior rim of the internal meatus the inter ureteric bar and its extensions over the intramural ureter and a mirror image of these lesions on the posterior bladder wall, the most dramatic of which is a midline lesion in which a rim of contused tissue encircles a small island of normal urothelium. These appearances resolve rapidly so that cystoscopy a week or more afterwards is likely to be entirely normal.

The consistency of location of the contusions suggests they are produced by the impact of the flaccid posterior bladder wall against the projections of the inter ureteric bar and internal meatus which in the male are thrown into

0002-8 03/80/060813 + 0 $00 20/0

prominence by the underlying mass of the prostate The prostate additionally transmits the counter impact of the rhythmic contraction of pelvic floor muscles in accompaniment of each step of the run At the instant of coming down on the foot the descent of the abdominal viscera forces the flaccid posterior wall of a nearly empty bladder into contact with its floor Although each impact itself is probably minor repetition during the course of a long run or jog produces trauma The bladder content is probably critical, since when it is completely empty both walls will be in apposition with no oscillation and therefore no impact of the surfaces whereas filling beyond a certain volume will ensure that the posterior bladder wall never contacts the trigone at any stage This critical volume is the likely explanation for the phenomenon being only an occasional or solitary event in someone who jogs regularly Bassler[2] has already drawn attention to prophylaxis in the form of a liter of beer before running or jogging[1]

The lesions in themselves are unimportant but knowledge of their occurrence provides the simple explanation for an alarming symptom The degree of exertion in jogging is unlikely otherwise to traumatize a normal urinary tract but may provoke bleeding from a renal or bladder tumor a renal cyst or hydronephrosis. The possibility of these occurrences necessitates upper and lower urinary tract investigation in all cases of hematuria following exercise

N J Blacklock M.D
Professor of Urological Surgery
University Hospital of South Manchester
Nell Lane West Didsbury
Manchester M20 8LR
England

REFERENCES

1 Blacklock, N J Bladder trauma in the long distance runner Am J Sports Med 7 239 1979
2 Bassler T J Beer as prevention for runner's haematuria Br Med J 2 1293 1979

Of pulmonary venous receptors

As indicated previously the heart is one organ made of two pumps (the right and left ventricles) These two pumps must be exquisitely synchronized to avoid serious circulatory disturbances, such as congestive heart failure (CHF) acute pulmonary edema and other circulatory problems The regulation of these two pumps must depend upon the central and autonomic nervous systems and associated extremely sensitive receptors in the pulmonary veins atria and superior and inferior venae cavae Some of the reflexes are already known—i.e the Bainbridge reflex but the receptors and reflexes in the pulmonary venous system are unknown or little known On the basis of physiologic logic and medical clinical theory there must be pulmonary venous receptors and reflexes which are major regulators of the synchronization of performance of the two pumps which constitute the heart The chemodectomas closely associated with the pulmonary veins and so common and widespread in the small pulmonary veins of patients with CHF surely represent hypertrophy from work of cardiac regulator receptors These regulators of the stroke volume and output of the right ventricle and left ventricle indicate the existence of normal pulmonary venous receptors and regulating reflexes yet to be anatomically and physiologically identified and defined

George E Burch M.D
Tulane University School of Medicine
and Charity Hospital of Louisiana
New Orleans La

REFERENCES

1 Burch G E Primer of Congestive Heart Failure Springfield Ill 1954 Charles C Thomas Publisher
2 Burch G E Congestive heart failure is not due to low cardiac output *per se* AM HEART J 94 769 1977
3 Ichinose H Hewitt R L, and Drapanas T Minute pulmonary chemodectoma Cancer 28 692 1971
4 Korn D Bensch K Leibow A A and Castleman B Multiple minute pulmonary tumors resembling chemodectomas Am. J Pathol 37 641 1960

Letters to the Editor

On Duroziez s disease

To the Editor

Ward concludes that the different patterns of acute and chronic valvular involvement being dependent on whether or not the patient had rheumatic fever suggest more than one etiologic agent may be responsible for what is currently regarded as a single entity—rheumatic heart disease The argument is as follows

The happenings [1] Of 248 children treated for acute rheumatic fever " Ward found that those with isolated carditis had a higher incidence of mitral systolic and mitral diastolic murmurs and cardiomegaly than those with arthralgia polyarthritis, and chorea Moreover the incidence of pericarditis was higher in those with isolated carditis, even when compared to the group with polyarthritis and comparable severe carditis. On the other hand those with isolated carditis had a lower incidence of subcutaneous nodules and aortic regurgitation than those with arthralgia and polyarthritis with comparable severe carditis

Of 296 patients with chronic valvular heart disease 164 had a history of rheumatic fever and 132 did not The former had a significantly higher incidence of mitral stenosis and regurgitation and aortic disease On the other hand, isolated mitral stenosis was much more common in those free of a history of acute rheumatic fever

The notion Ward reasoned that "If all cases of acute valvulitis have a common etiology they should have either similar clinical features or fit into a definable clinical syndrome and in chronic valvular heart disease the pattern of valvular involvement should not be affected by the presence or absence of a rheumatic history Ward concludes therefore that isolated mitral stenosis is not commonly a sequela of acute rheumatic fever

The name Therefore Ward concludes that the label rheumatic valvular heart disease" should be restricted to incidences with a history of acute rheumatic fever and that isolated mitral stenosis without a past history of acute rheumatic fever does not merit the name rheumatic heart disease If a name for isolated mitral stenosis of unknown cause is wanted I suggest resurecting Duroziez s disease[3] after the clinician who on the basis of his clinical observations, came to the conclusion that at least half of all subjects with isolated mitral stenosis did not have rheumatic heart disease Vaquez[4] devotes an entire chapter on this disorder in his classic book on diseases of the heart

Comment The history of medicine is replete with examples *that prove that Ward s notions are not always correct* Markedly dissimilar clinical disorders may be due to a common etiology (e g meningococcemia and meningococcic meningitis) and similar clinical syndromes may be due to diverse etiologies (e g pernicious aenemia "Bright s disease") Manifestations of a clinical disorder (disease) depend upon the reaction of an individual to his total environment including the essential (etiologic) agent

Nevertheless, Ward I think, is correct when he demands evidence for the inference that isolated mitral stenosis is necessarily always of rheumatic origin One cannot use architectural evidence because there are infinite deleterious agents and only a finite number of ways that tissues can respond to injury Furthermore mitral val e surgery for isolated mitral stenosis and death due to this disorder occur so long after the development of the lesion that immunological abnormalities and inflammatory changes that may have been present soon after the onset of the acute illness are no longer present One must therefore turn to observations of clinicians who have followed subjects closely both before and after the onset of clinically recognized isolated mitral stenosis.

Walsh, Bland and Jones have done this. They report on 48 patients who have been observed before and after the stage of pure mitral stenosis and in 33 only after the signs of pure mitral stenosis were already established. Of the 48 27 initially had signs of mitral regurgitation with or without signs of other lesions The other 21 had no detectable valvular disease after recovery from their acute illness Of these two developed mitral regurgitation three developed mitral regurgitation and stenosis but later developed signs of pure isolated mitral stenosis. But in 16 patients (79) the valvular lesion began and remained as pure isolated mitral stenosis years after the acute illness It is particularly to be noted that most of these patients were considered to have a mild form of rheumatic fever on the basis of the absence of a recognizable illness prior to the appearance of heart disease in four a period of poor health of obscure nature immediately preceding the appearance of heart disease in three and in addition to poor health, either characteristic joint pains or chorea in the remainder The conclude "In some of their younger patients who were under close observation at the time of their active disease it had been impossible to identify clearly as rheumatic fever their mild illness prior to the appearance of characteristic signs (of mitral stenosis) in the heart "[5]

In her classic monograph, May Wilson wrote Cardiac abnormalities in the absence of a history or evidence of rheumatic fever do not warrant a diagnosis of rheumatic heart disease " No one adheres to this dictum even when inflammatory and immunologic evidence is lacking

The mitral valve would indeed be unique if only one cause were responsible for the development of mitral stenosis Burch and Ward and others have already obtained evidence supporting other causes. From the pragmatic standpoint one must decide whether anything is gained or lost by the gratuitous addition of the label "rheumatic "

Louis A Soloff M.D
Division of Cardiology
Temple University Health Sciences
Center 3401 North Broad St
Philadelphia Pa 19140

REFERENCES

1 Ward C A reappraisal of the clinical features in acute and chronic rheumatic heart disease Etiologic implications, AM HEART J 98 298 1979
2 Crookshank, F G *in* The Meaning of Meaning, Ogden, C K., and Richards I A. New York 1944 Harcourt Brace and Company 6th edition
3 Duroziez, P L. Traite des maladies du couer Paris, 1891
4 Vaques, H Diseases of the Heart Translated by G F Laidlaw Philadelphia 1924 W B Saunders Company 1924
5 Walsh, B J Bland E F., and Jones, T D Pure mitral stenosis in young people Arch. Intern. Med. 65 321 1940
6 Wilson M G Rheumatic Fever The Commonwealth Fund, London 1940 Oxford University Press

Incidence of thrombocytopenia in medical patients on mini dose heparin prophylaxis

To the Editor

Prophylactic low dose subcutaneously administered heparin has been increasingly advocated and utilized in high risk surgical and medical patients groups However there have been a number of recent reports of thrombocytopenia occurring during the course of therapeutic heparin administration[1] some associated with serious sequellae Thus in one prospective study it was reported that 31% of patients on continuous heparin infusion had significant thrombocytopenia and routine platelet counts have been advocated to identify this problem when it occurs Anecdotal accounts of thrombocytopenia in patients on low dose subcutaneous heparin utilized prophylactically have also recently been reported raising the question of how prevalent and clinically common the complication of thrombocytopenia is with low dose prophylactic heparin To date and to the best of our knowledge the complications of subcutaneous prophylactic heparin have only been analyzed carefully in surgical patients In an attempt to further investigate this problem we performed a prospective study of patients on low dose subcutaneous prophylactic heparin in a medical service to determine the frequency of thrombocytopenia

From November 1978 to April 1979 50 male patients received subcutaneous prophylactic heparin for at least 5 days while on the medical Service at the Salt Lake City Veterans Administration Medical Center The decision to treat was based on clinical indications in each patient made entirely by the ward hou[illegible] ring for the patient Baseline platelet counts were obtained prior to heparin administration and then on a daily basis excluding weekends Informed consent was obtained Platelet counts were done in triplicate by the Coulter counter method and the average of three counts was used Significant thrombocytopenia was defined as a 30% decrease in platelet count from our baseline values The daily heparin dose prescribed was left to the discretion of the ward staff with 26 patients (52%) receiving 5 000 U S P units every eight hours and 24 patients (48%) receiving 5 000 U S P units every 12 hours The patients diagnoses were noted as were the indications for treatment

Results showed that in the 50 male patients only three (6%) had a significant fall in platelet count One of these patients was receiving radiation therapy for a lung tumor during which platelet counts fell gradually consistent with radiation toxicity In another patient septic shock was the probable cause of thrombocytopenia In the third patient no obvious alternative explanation could be incriminated Thus the incidence of thrombocytopenia in our study is probably 2% This contrasts with the 31% incidence reported by Bell and associates in patients receiving heparin in *therapeutic* dosage

Our results suggest that thrombocytopenia secondary to subcutaneous low dose heparin is an unusual complication in male medical patients Thus we disagree with some authors who suggested daily or frequent platelet counts be obtained on all patients on heparin—at least for male patients such as occur at Veterans Administration Medical Centers who receive low dose heparin Obviously such surveillance would be quite expensive considering the increasing utilization of subcutaneous low dose heparin prophylaxis We suggest the alternative that male patients on subcutaneous low dose heparin be watched carefully for clinical evidence of thrombocytopenia (i e bleeding petechiae) and in the event these occur then platelet counts should be obtained Because our study only included male patients it is not clear to what extent these data are valid for female patients

Garrison H Ayars M D
Gerasim Tikoff M D
Department of Internal Medicine
University of Utah College of Medicine
The Medical Service of the Veterans Administration Medical Center
Salt Lake City Utah 84148

REFERENCES

1 Bell W R Tamaseilo P A Alving B and Duffy T P Thrombocytopenia occurring with the administration of heparin Ann Intern Med 85 155 1976
2 Rhodes G R Dixon R H and Silver D Heparin induced thrombocytopenia Ann Surg 186 752 1977
3 Klein H G and Bell W R Disseminated intravascular coagulation during heparin therapy Ann Intern Med 80 477 1974
4 Hrushesky W J Subcutaneous heparin induced thrombocytopenia Arch Intern Med 138 1489 1978
5 Hrushesky W J Thrombocytopenia induced by low dose subcutaneous heparin (Letter) Lancet 2 1286 1977
6 Rocko J M, Mikhail F Trilles F and Timmes J J The safety of low dose heparin propylaxis Am J Sur 135 798 1978
7 Nelson J C Lerner R G Goldstein R, and Cagin N A Heparin induced thrombocytopenia Arch Intern Med 138 548 1978
8 Bell W R Thrombocytopenia occurring during heparin therapy N Engl J Med 295 276 1976

Cost of continuous infusion vs intermittent IV heparin

To the Editor

In a recent study in THIS JOURNAL Wilson and Lampman concurred with Mant and associates that the incidence of major bleeding is not significantly different with continuous infusion or intermittent intravenous (IV) heparin Although more study is needed to resolve this controversy if the safety and efficacy are virtually the same for both methods of administration of heparin then the cost of each method needs analysis

In order to demonstrate the potential savings that can be gained with the use of intermittent IV heparin therapy two commonly recommended heparin regimens for pulmonary embolism or deep vein thrombosis were compared

Cost analysis of two common heparin regimens is found in Tables I and II

Comparing the hospital cost of each ten day regimen at list price a savings of $114 06 is realized Patient charges of course would far exceed this amount

When a hospital savings of approximately $100 in one patient are applied on a national scale the potential savings are significant Wessler estimated that 250 000 cases of

Table I Regimen one (intermittent therapy) Heparin 5 000 units intravenous bolus immediately followed by 5 000 units intravenous bolus every 4 hours for ten days[7,8]

	Hospital cost (24 hours)	Hospital cost (10 days)
Heparin 5 000 units q4h	$4 14	$41 40
Needles and syringes	0 72 ($0 12/unit)	7 20
Heparin 5 000 units (immediate one time dose)		0 69
Small vein infusion set for intermittent administration (changed every two days)	0 43 ($0 85 set cost)	4.25
Total course		$53.54

Table II Regimen two (continuous infusion therapy) Heparin 5 000 units immediate intravenous bolus followed by Heparin 10 000 units in 5% dextrose in water 500 ml to run every 10 hours (1000 units/hour via infusion instrument[7,8])

	Hospital cost (24 hours)	Hospital cost (10 days)
Heparin 1 000 units/hour	$3 31	$ 33 31
Heparin 5 000 units (immediate dose)		0 69
DW5 500 mL at 50 ml /hr	6 12	61 20
Needle and syringe	0.24 (2 units/24 hrs)	2 40
Standard administration set (changed every 2 days)	0 66 (1.31 set cost)	6 55
Final filter (0 5 micron)	0 99 (1 97 filter co t)	9 85
Small vein infusion set (changed every 2 days)	0 36 (72 set cost)	3 60
Infusion pump	5 00	50 00
Total Course		$167 60

Cost of controlled infus on device will v ry w th type nd brand of nfusi n in trum nt used and if speci l dministrat on sets are required.

pulmonary embolism are hospitalized in the U S annually Coon and colleagues reported that there are approximately 250 000 clinically recognized cases of deep vein thrombosis in the U S each year Assuming only half of these patients recei e intermi tent heparin therapy (vs continuous infusion) as described above there could b an approximate hospital savings of 25 million dollars. Patient and third party payer savings would obviously be even more significant.

Other factors that need to be con idered in a discussion on hospital costs for heparin administration include nursing personnel time for site care monitoring and rate adjustments of intravenous solutions for continuous administration versus the personnel time required for intermittent site care and the time required for an intravenous bolus Mant and colleagues and Rosenblum allude to the fact that use of intermittent administration is generally *less complex than continuous* infusion Nurses of the intravenous therapy team at the University of Tennessee Hospital Memphis prefer the intra e nous bolus route over the continuous infusion for ease of administration and because there is less potential for error

Additionally laboratory tests under most situations would also be similar for either intravenous continuous or intermittent administration It al o must be mentioned in a discussion of heparin costs that many patients receive less than a 10-day course of heparin therapy (minimum course 7 days)

If further investigations concur with the work of Mant and colleagues and Wilson and Lampman (intermittent intravenous administration of heparin is as safe and effective as continuous infusion) we believe because of the potential cost savings intermittent heparin therapy to be the preferred method of administration

More study is needed to resolve the controversy over which method is preferred However as with other drug therapies if safety and efficacy are quite similar then cost of over all therapy must be assessed

Timothy H Self Pharm D
Ross E Vanderbush Pharm D
Department of Pharmacy Practice
University of Tennessee
Center for the Health Sciences
8 4 Union Ave
Memphis Tenn 38163

ENCES

1 Wilson J R., and Lampman J Heparin therapy A randomized prospective study Am Heart J 97 155 1979

2 Mant M J Thong K L Birtwhistle R V et al Haemorrhagic complications of heparin therapy Lancet 1 1133 1977

3 Salzman E W., Deykin D Shapiro R M and Rosenberg R Management of heparin therapy N Engl J Med 292 1046 1975

Glazier R L and Crowell E B Randomized prospective trial of continuous vs intermittent heparin therapy JAMA 236 1365 1976

Sasahara A A. Therapy for pulmonary embolism JAMA 229 1795 1974

Moser K M, State of the art Pulmonary embolism Am Rev Resp Dis 115 829 1977

Red Book 1979 Oradell NJ 1979 Medical Economics Co page 227

Hospital Price List and Ordering Information Effective February 1 1979 Travenol Laboratories Inc One Baxter Parkway Deerfield Illinois 60015

Wessler S Venous thromboembolism Scope of the problem *in* Prophylactic Therapy of Deep Vein Thrombosis and Pulmonary Embolism Fratantoni J and Wessler S coeditors Washington DC 1975 DHEW Publication No (NIH) 76 866 p 1

Coon W W Willis P W III and Keller J B Venous thromboembolism and other venous disease in the Tecumseh Community Health Study Circulation 48 839 1973

11 Rosenblum D Bleeding and clotting disorders and anticoagulation *in* Manual of Medical Therapeutics Boedeker E C., and Dauber J H eds Boston 1974 21st edition Little Brown and Company p 302

Reply

To the Editor

Doctors Self and Vanderbush have shown that equipment and labor inputs for the intermittent method of heparin administration may be quite a bit less than for the continuous method This is an undeniably pertinent fact bearing on the choice of a preferred method

Our study suggested that neither method had a clear advantage in reducing risk of serious hemorrhage The small numbers of patients in this study limits the certainty with which this conclusion is justified Nevertheless, until convincing evidence of less efficacy or greater risk is presented we would agree that it is quite reasonable to recommend the intermittent method on the basis of economic considerations

James H Lampman MD
John R Wilson MD
Cuyahoga County Hospital
3395 Scranton Rd
Cleveland Ohio 44109

Book reviews

Exercise and Coronary Heart Disease By Gerald F Fletcher and John D Cantwell, Springfield Ill. 1979 Charles C Thomas, Publisher 340 pages, Price $27.50

This publication concerned with exercise and coronary heart disease consists of 14 chapters which review fairly completely the relationship of sedentary living and exercise to coronary heart disease Among the subjects discussed are historical aspects exercise physiology exercise as a risk factor lack of exercise as a risk factor dangers of exercise and rehabilitation A list of cardiac rehabilitation centers is included in Chapter 12 The present emphasis on exercise and rehabilitation makes this book timely Readers will find the information interesting This reviewer is of the opinion that physicians who treat the patients with coronary heart disease are best qualified to manage rehabilitation in each individual patient. They know them best This book can assist doctors in outlining exercise training and advice The book fails to provide convincing data as to whether or not exercise increases longevity Readers certainly will learn from this book the trends in exercise advice given patients The photograph of Paul White on page 5 is interesting

Management of Ventricular Tachycardia—Role of Mexiletine Proceedings of a Symposium held in Copenhagen May 25 27 1978 Edited by E Sandoe D G Julian and J W Bell Copenhagen 1978 61? pages.

This is the proceedings of a symposium held in Copenhagen during May 1978 on a relatively new antiarrhythmic drug The book is extensive It includes many papers on ventricular tachyarrhythmias in particular The pathophysiology of the arrhythmias, electrophysiology of the arrhythmias and drug action choice of drugs role of beta blockade and use of mexiletine are among the many subjects discussed This is a very detailed review of the ventricular tachyarrhythmias an extremely important problem in clinical practice Those who study this publication will profit considerably from the time devoted It is not an easy book to read or study Nevertheless it is a good book for all physicians not only for cardiologists

Electrocardiographie Pratique—Second Edition By R. Rulliere Paris 1978 Editions Masson 532 pages

This book in French is the second edition It consists of a series of electrocardiograms recorded on patients with various clinical cardiac states The clinical data on each patient which justified the recording of the tracing are briefly presented A brief history and physical findings are presented The electrocardiogram is interpreted and a brief comment is finally included to indicate the role of the ECG in the management of the patient s clinical state The tracings are very good, the measurements are accurate and the role of the tracing in the clinical study is discussed clearly Those who are learning the use of the electrocardiogram in clinical practice will find this to be a good book. Nevertheless, to appreciate the tracings and their applications it is best the reader should have a good background knowledge of the fundamentals of electrocardiography The tracings are grouped into 14 different syndromes such as that found in patients with dyspnea on effort, brief periods of chest discomfort prolonged periods of discomfort palpitation syncope hypertension large hearts cyanosis and others. This is an interesting book and a good one for the study of clinical cardiology and electrocardiography by means of discussions of patients.

Cardiology By D G Julian New York, 1978 Macmillan Publishing Company Inc 347 pages Price $13 00

This paperback book is a good review in a few pages of the essentials of clinical cardiology Those who have learned the physiology and pathology of the heart and circulation can profit most from this fine small book It is in its third edition an indication of its previous reception The field of clinical cardiology is presented clearly and concisely for the benefit of the busy physician This is a good book.

Books received

Manual of Emergency and Outpatient Techniques Edited by Allen P Klippel M D and Charles B Anderson M D Boston 1979 Little Brown & Company 433 pages Price $10.95

Noninvasive Approaches to Cardiovascular Diagnosis By Alfred F Parisi and Donald E Tow New York 1979 Appleton Century Crofts Inc 241 pages Price $12.95

Progress in Pharmacology Vol 2 No 2 By H Lullmann T Peters M J Mattila, and V M K Venho Stuttgart & New York, 1979 Gustav Fischer Verlag 86 pages Price $26 00

Recovery of Reality Overcoming Chemical Dependency By George A Mann M D New York, 1979 Harper & Row 180 pages. Price $8 95

Body Imaging Conference

The Fifth Annual International Body Imaging Conference will be held at the Kauai Surf Hotel, Kauai Hawaii, October 11 through 1[illegible] 1980 The conference offers approximately 25 Category I A MA credits and will present to participants a correlated approach to the principles, indications uses interpretation and results obtained with computed tomography ultrasonography and nuclear imaging Course participation by practicing imaging physicians, residents, technologists and corporate personnel is encouraged Fees for registration are $3[illegible] ([illegible]) for physicians and $23[illegible] for residents and technologists with letter registration is limited Registration and inquiries should be addressed to Conference Secretary Fifth Annual International Body Imaging Conference West Park Hospital Dept of Radiology 22141 Roscoe Blvd Canoga Park Calif 91[illegible]

Symposium on Cardiac Arrhythmias and Conduction Defects

A symposium entitled Electrophysiology of Cardiac Arrhythmias and Conduction Defects" will be presented at the Detroit [illegible] Hotel Detroit on September 25 through 27 1980 The symposium is sponsored by the Michigan Heart Association and the Council on Clinical Cardiology of the American Heart Association the Course Director is Seymour Gordon M D For further information contact Michigan Heart Association P O Box LV 160 Southfield Mich 48076 Telephone (31[illegible]) [illegible]9[illegible]00 for Eleanor D Peterson R N

Health Sciences Communications Association

Health Sciences Communications Association will hold its 22nd Annual Convention in Galgary Canada on June 14 through 18 1980 The convention theme is Images for Health For further information contact Stuart Winn, Co-ordinator Education Services Faculty of Health Sciences, McMaster University 1200 Main St West Hamilton Ontario Canada L8S 4J9

International Meeting on Cardioplegia and Myocardial Protection

This symposium will be held in London England on June 9 and 10 1980 and will cover recent advances in the understanding of basic mechanisms of ischemic injury and the prevention or reduction of tissue damage during open heart surgery using the techniques of chemical cardioplegia and hypothermia Methods of investigation of myocardial damage will be assessed as will the rationale of formulation and use of cardioplegia solutions. In addition to an international list of speakers participation is invited by delegates For further information please contact Advisory Services Medical Symposia 79 Wimpole Street London W1M 7DD England.

IMPORTANT
INFORMATION FOR AUTHORS

Effective June 1 1980 all manuscripts for the AMERICAN HEART JOURNAL should be sent to

Dean T Mason M D
Section of Cardiovascular Medicine
University of California
School of Medicine
Davis California 95616

American Heart Journal

An international publication for the study of the circulation

George E Burch *Editor*
James A Cronvich *Assistant Editor*
Peter C Gazes *Assistant Editor*

VOLUME 99

JANUARY-JUNE 1980

Author index*

T

U

V

W

Subject index*

*January pp 1 138 Feb .. .. .. 8 March pp 279-408 April pp 409-546 May pp 547 682 June pp 683-840

B

D

E

F

G

H

I

Q

R

S

T